FINAL REPORT

Economic Analysis of the Impact of Isolated Human Gene Patents

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IP Australia

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THE CENTRE FOR INTERNATIONAL ECONOMICS
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Glossary

Glossary of terms

Term	Definition
AusPat	An online repository of patents and applications filed in Australia.
Ceased	A granted patent that has not had its renewal fees paid by the applicant.
Complimentary DNA (cDNA)	cDNA refers to an isolated gene sequence that has been isolated in the laboratory and differs from the natural state as it does not include introns (the non-coding segments of a genomic sequence).
Counterpart in nature	Term to describe claimed isolated gene sequences that would be found naturally in nature. Refers to isolated genomic DNA or genomic clones.
Diagnostic claims	Diagnosis (use of the gene or protein sequence to diagnose or prognose disease or disorders associated with the gene (diagnostic kit/assay/probe).
DNA	DNA (Deoxyribonucleic acid) carries genetic information and is a double stranded polymer.
Domestic Applicants	Applicants for patent applications from entities or individuals that are Australian.
Earliest Priority Date	The earliest priority date refers to the earliest filing date and it is this date when patentability is assessed (novelty and inventive step). This will differ to the filing date when an applicant files in another country and uses that date as the priority date, or when a provisional application is filed.
Expired	A granted patent has lived its full term of protection.
Filing Date	The date a complete application is submitted to the Australian Patent Office
First IPC Mark	The first IPC Mark assigned to a patent, more than one Mark is assigned.
Full-length isolated gene sequence	These full-length sequences encode a human protein.
Gene	A gene is a discrete segment of DNA that carries information for the amino acid sequence of a protein. A nucleic acid is a molecule composed of nucleotide sub-units, such as DNA or RNA. Other names include polynucleotides, DNA or RNA sequence.
Genomic DNA (gDNA)	gDNA or genomic clone is the isolated gene sequence that is naturally found in humans.

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Term	Definition
Granted	Once a patent application has been granted, the file is sealed and the patent is referred to as being 'in force'.
Human Genome Project (HGP)	The Human Genome Project was an international project coordinated by the National Institutes of Health (U.S.) with the aim to identify all genes in the human DNA. The first draft was published in 2001 and the project was completed in 2003. The analysis of the database is still ongoing and successor projects have been established to achieve this.
International Applicants	Applicants for patent applications from entities or individuals from overseas.
IMS	IMS is a leading provider of information, services and technology for the healthcare industry, covering markets in over 100 countries around the world.
International Patent Classification (IPC) Mark	The IPC is an indexing system based on the technology of the patents established by the Strasbourg Agreement 1971 and maintained by the World Intellectual Property Organization (WIPO).
Method claims	These claims only include the use of a product (isolated gene sequence).
Method only (use)	These claims do not cover an isolated gene sequence, but rather, only the use of an isolated gene sequence for normally diagnostic and therapeutic purposes
Modified antibody	A modified differs from the antibodies found naturally in human immune systems. These antibodies are engineered using modified isolated gene sequence to express a protein product (the antibody) for therapeutic/diagnostic purposes. A modified antibody has the ability to bind a target with great specificity and can bind to, or prevent, the function of certain targets or it can be used to detect targets.
Modified isolated gene sequence	A sequence that has been altered in some way from its naturally occurring counterpart, for example, the isolated gene sequence is altered to code for an altered protein with improved properties from the wildtype. These isolated gene sequences do not have a counterpart in nature.
No counterpart in nature	Term to describe claimed isolated gene sequences that are only derived from nature, and are not parallel in nature. Refers to isolated complimentary DNA and products can include modified antibodies and other modified isolated gene sequences, as well as sequences that are partial only.
No longer in force	Granted patents that are classified as 'Expired', 'Ceased' or 'Revoked'. These patents are no longer enforceable by law.
Partial isolated gene sequence	These partial sequences includes probes and primers and are only fragments/segments of the whole gene.

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Term	Definition
Patents	Granted patents that can exclude others from the use and sale of the patented product or method.
Priority date	Priority date refers to the earliest filing date, and it is this date when patentability is assessed.
Private Applicant	An entity including biotechnology, pharmaceutical and private diagnostic companies.
Product claims	These claims include the isolated gene sequence itself, either in whole or in part, and claims to various products obtained using the sequence.
Provisional application	This is used to establish the 'priority date' of an invention. Complete applications must be filed within 12 months.
Public Applicant	An entity including hospitals, universities, medical research institutes (MRI's) and other government organisations.
Recombinant DNA	A laboratory process where an artificial gene (recombinant gene) is isolated. It is then used to express its encoded protein (recombinant protein expression).
Revoked	A granted patent has been terminated by the Australian Patent Office.
RNA	RNA (Ribonucleic Acid) is a single stranded nucleic acid molecule and mRNA (messenger RNA) is transcribed from DNA and is the template for protein synthesis.
Status	The status of a patent or patent application.
Still in force	Granted patents. These patents are enforceable by law.
Therapeutic claims	The use of an isolated gene sequence to treat disease, in some cases using the gene itself (gene therapy) or indirectly by identifying molecules that modulate or interact with the gene (for example small molecule drugs)

Source: The CIE.

Glossary of Acronyms

Acronym	Definition
AHMAC	Australian Health Ministers' Advisory Council
AIHW	Australian Institute of Health and Welfare
ALRC	Australian Law Reform Commission
APEC	Asia-Pacific Economic Cooperation
APOE	Apolipoprotein E gene
ARC	Australian Research Council
AUSFTA	Australia-United States Free Trade Agreement
BRCA1	Breast Cancer susceptibility gene 1
BRCA2	Breast Cancer susceptibility gene 2
cDNA	Complimentary DNA refers to a gene sequence that has been isolated in the laboratory and differs from the natural state, as it does not include introns (the non-coding segments of a genomic sequence).
CF	Cystic Fibrosis
CNS	Central Nervous System
CRC	Cooperative Research Centres
CSIRO	Commonwealth Scientific and Industrial Research Organisation
DEST	Department of Education Science and Training
DIISRTE	Department of Industry, Innovation, Science, Research and Tertiary Education
DNA	DNA (Deoxyribonucleic Acid) carries genetic information and is a double stranded polymer.
DoHA	Department of Health and Ageing
EPO	European Patent Office
ESHG	European Society of Human Genetics
ESTs	Expressed Sequence Tags
FDA	Food and Drug Administration
gDNA	Genomic DNA or genomic clone is the gene sequence that is naturally found in humans.
GDP	Gross Domestic Product
HFE	Hereditary Haemachromatosis gene
HGP	Human Genome Project
HPV	Human Papillomavirus
ICGC	International Cancer Genome Consortium
IP	Intellectual Property
IPC Mark	The International Patent Classification is an indexing system based on the technology of the patents established by the Strasbourg Agreement 1971 and maintained by the World Intellectual Property Organization (WIPO).

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Acronym	Definition
IPEG	Intellectual Property Expert's Group
IPR	Intellectual Property Right
IPRA	Intellectual Property Research Institute of Australia
LOAs	Licences, Options and Assignments
LQTS	Long QT Syndrome
MBS	Medicare Benefit Scheme
MRI	Medical Research Institutes
mRNA	Messenger RNA, these molecules convey genetic information from the DNA to the ribosome.
NHGRI	National Human Genome Research Institute
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health
NME	New Molecular Entity
NRDC	National Research Development Corporation
NTD	Neglected Tropical Disease
OECD	Organisation for Economic Co-operation and Development
PBRs	Plant Breeders Rights
PBS	Pharmaceutical Benefit Scheme
PCR	Polymerase Chain Reaction, laboratory technique to amplify DNA sequences.
PCT	Patent Cooperation Treaty
R & D	Research and Development
RCPA	Royal College of Pathologists of Australasia
RNA	RNA (Ribonucleic Acid) is a single stranded nucleic acid molecule and mRNA (messenger RNA) is transcribed from DNA and is the template for protein synthesis.
SACGHS	Secretary's Advisory Committee on Genetics, Health, and Society
TGA	Therapeutic Goods Administration
TRIPS	Trade-Related Aspects of Intellectual Property Rights
USPTO	United States Patent Office
WTO	World Trade Organization

Source: The CIE.

Summary

This report fills key gaps in the existing literature to review the economic impact of isolated human gene patents — their impact on incentives and disincentives to undertake and commercialise research.

Key findings:

- **Patent activity related to isolated human gene sequence patents has declined dramatically since the completion of the Human Genome Project in 2003. Current patent activity focuses most on modified gene sequences or method only claims.**
- **Measurable economic impacts associated with isolated human gene sequence patents are small in terms of royalty and fee income that is attributable to the patent.**
- **The real value in patents lies in their role in incentivising innovation and the public-private partnerships that are required to bring new human gene based medicines and diagnostics to market that ultimately improve health outcomes.**
- **Reflecting changes in patent activity, increasingly the patents involved are those that are not isolated human gene sequence patents.**

About isolated human gene patents

As with all patents, there are challenges and trade-offs when temporary exclusive rights are required to spur innovation — isolated human gene sequence patents are no different.

There are varying views on the merits of isolated human gene sequence patents. Where proponents claim that patents are crucial to supporting high risk and high cost medical discovery and development, critics are concerned about how they might limit the accessibility and inflate the price of healthcare and diagnostic services.

For the purpose of this study, isolated human gene sequence patents are those that include at least one claim to an isolated human gene sequence or a portion or fragment of an isolated human gene sequence. Patents related to isolated human genes that cover only methods of use or modified gene sequences are not the focus of this study, and are therefore excluded from our definition.

The area of human genetics research is relatively new and rapidly evolving, with case law and patents coinciding with progress in scientific discovery.

The objectives of isolated human gene sequence patents are fundamentally economic — to encourage investment in useful technologies and promote innovation through the

diffusion of knowledge and the incentive of a legally enforceable exclusive right to commercially exploit the invention for a set period.

Defining the isolated human gene patenting industry in the Australian economy

Human genetics research in Australia is a partnership between public and private investment — as is the case with other areas of research in Australia, government invests in early stage basic research and commercial entities take on the risks and rewards required to bring new innovations to market.

Human genetic research involves a wide range of entities in upstream basic research through to downstream commercialisation activities in the human genetics area. The 'isolated human gene patenting industry' in Australia includes:

- entities involved in basic research undertaken largely by universities, Medical Research Institutes (MRIs) and Cooperative Research Centres (CRCs), which are funded through a variety of Commonwealth and State government channels;
- entities involved in early stage translational research, undertaken by biotechnology companies, university spin off companies, and various partnerships between universities, MRIs, pharmaceutical and biotechnology companies; and
- entities involved in commercial research, including clinical trials across various phases, mainly Phase 3 clinical trials.

We estimate that at least $795 million annually is being invested in research and development (R&D) associated with human genes in Australia, around 21 per cent of which is estimated to be private sector investment (for profit and not-for-profit).

Most of this research (79 per cent, or approximately $628 million) is funded by government, and is more akin to basic research where inventions are yet to be identified and research is often published and widely disclosed.

This is as opposed to downstream research, where patents are more critical and intellectual property needs to be protected to ensure ongoing investment to translate findings into new medicines and treatments. A key challenge is that it is impossible to know which patent will ultimately underpin new medicines, and in some cases, it will be the upstream patent that matters.

The Australian pharmaceutical and biotechnology sector invests the balance of total human gene related R&D (approximately $167 million annually). While it is not possible to apportion this between isolated human gene sequence research and research related to modified human DNA technologies, some R&D would be specially related to research underpinned by isolated human gene patents. Spillover benefits associated with private pharmaceutical R&D have been found to range from 25 cents to 80.5 cents in the dollar of all spending, depending on the type of R&D performed.

Businesses involved in human genetic research contribute to economic activity in Australia and are making an important and growing contribution to the broader medicines sector.

In 2011–12, medicinal and pharmaceutical product exports totalled over $4 billion. There are over 300 biotechnology companies in Australia that focus specifically on human therapeutics and diagnostics and over 500 biotechnology companies in total operating in Australia. Approximately 41 000 people are employed in pharmaceutical manufacturing, wholesaling, R&D and biotechnology. A subset of this private sector activity would relate to private investment in human genetics R&D in Australia.

Based on the Revealed Technological Advantage (RTA) index from United States Patent and Trademark Office (USPTO), Australians have a comparative advantage in patenting biotechnology in the US relative to the rest of the world, and have had for some years.

There are currently over 1000 full time equivalent people employed in medical genetic laboratories in Australia involved in human genetic testing, which is specifically related to human genetics-related activities.

An estimated 15 per cent of pharmaceutical and biotechnology business expenditure on R&D in Australia is foreign direct investment (FDI), which points to FDI on human genetic research in Australia in the order of $25 million annually.

Estimating the financial value of isolated human gene patents

The direct financial returns to an isolated human gene sequence patent are relatively modest and arise only when patent holders seek to sell access to their invention. The real value of patents is in attracting the private capital required to take on the risks of translational R&D, and ultimately the availability of better treatments for consumers that improve population health.

Not all isolated human gene sequence patents result in a commercially viable product. The significance of the temporary exclusivity afforded by patents depends, among other things, on:

- the success of later stage (downstream) research;
- the cost effectiveness of translating patented inventions into medicines, diagnostics and vaccines; and
- the role of the patent in securing the capital investment required for research, given that the vast majority of early stage (upstream) human genetic research is unlikely to be funded by revenue from product sales.

The value of patents is judged by their ability to encourage the availability of new and useful technologies to society, and to encourage innovation through encouraging the diffusion of knowledge beyond which would be the case in their absence.

The financial value of a patent depends in large part on how the patent holder exploits its patent right:

- *direct* economic benefits can accrue to patent holders from the additional cash flow created by exercised patent rights when non-patent holders are permitted access to the patent; and
- *indirect* economic benefits can be derived from many factors, such as the signal that patents provide regarding R&D strength which help patent holders to raise investment

capital, market advantages obtained defensively to prevent competitors from obtaining similar patents and to raise the costs for competitors to enter a given market, and improve health outcomes as a result of access to pharmaceuticals and clinical practice that deliver net social (improved health and wellbeing) and economic (improved productivity and workforce participation) benefits.

The total annual revenue to Australian holders of isolated human gene patents is relatively modest and estimated (with 95 per cent confidence) to be between $1.1 million and $2.6 million annually, although there is huge variation in returns.

For instance, across all patent types held by publicly funded research institutes, approximately 30 per cent of Australian patents generate *no income* to patent holders from licensing, options or assignments (LOAs). Over 20 per cent generate less than $250 000 annually in returns, and some outliers may accrue over $100 million.

Expenditure on pharmaceutical and other health care goods relating to isolated human gene patenting

There are several components to the effective price paid for medicines, diagnostics, vaccines, and treatment methods that are underpinned by an isolated human gene sequence patent and/or patents over modified or recombinant DNA technologies. They include taxpayer investment in basic research, payments for access to patented inventions, and price premiums for final products. Each of these components map a different stage of the research — development continuum, and the particular risks and rewards that exist at that stage.

As set out above, the Australian government invests a great deal in human genetic research, and some patent holders charge others for access to patented inventions. When end products become available to consumers, patent holders may also realise price premiums for products that are underpinned by an upstream isolated human gene patent.

Data on the isolated human gene patent status of pharmaceuticals and diagnostics available in Australia is difficult to obtain or derive, partly due to the complexity and opaqueness of the pricing process.

For instance, while there are over 500 molecular genetic tests available in Australia, most diagnostic testing is funded by State governments in block funding arrangements with public hospitals.

Only a very small subset of tests are funded by the Medicare Benefits Schedule (MBS), which separately identifies expenditure by test type. In 2011–12, MBS expenditure for the two tests that have an active patent was $3.1 million.

A broader (non-MBS specific) analysis of 37 identifiable genetic tests with, and without, a patent suggests that a price premium is paid for patent-related genetic tests (with an average price for patented tests of $538 compared to $346 for non-patented tests). This estimate is considered illustrative, but not conclusive, due to data limitations and the multiple factors affecting test costs.

Effects on competition and innovation

There are substantial barriers and commercial hurdles involved in converting an invention within an isolated human gene patent into a final product. Patents are one (albeit important) element of the regulatory framework for providing access to new and better treatments for consumers. Like all interventions, patents can create a trade-off between innovation and competition for a defined period.

Patents are important to recouping high development and commercialisation costs, enabling the transfer of technology between researchers and companies operating at different stages of the research-development continuum. Patents also provide the certainty required in a business characterised by high costs, large unrecoverable costs, and various scientific, technology, production and commercialisation risks.

Research and development costs for biologics (which are most likely to be underpinned by an isolated human gene sequence patent) are estimated to be between US$1.4–US$1.9 billion per new molecular entity. Lead times from successful research outcomes to regulatory product approval are extensive, with around 10 to 12 years to get a new product to market.

Risks and uncertainties produce high failure rates and only 30 per cent of drugs entering clinical testing will reach the market. Hence, an estimated 70 per cent of expenditure per successful drug is spent on failed projects and is therefore a 'sunk' unrecoverable cost.

This is not ordinarily the case for diagnostics, as once the isolated gene sequence for a particular disease related gene has been identified and isolated, the development of the test is not as onerous as it is for medicines. There are different regulatory frameworks governing the approval and listing of diagnostics and pharmaceuticals. While both are required to satisfy a clinical efficacy, the process of doing so is more onerous (and costly) for pharmaceuticals than for diagnostics.

Despite the importance of patents to the business model of bringing health care innovations to market, patents can, and in some cases do, bring trade-offs.

These include actual or potential blockages and restrictions to research, compliance and enforcement costs, which exist whether or not the patent has any market value, and costs associated with the lack of competition which is embedded in the IPR regime.

Some case studies highlight examples where isolated human gene sequence patents have limited access to patented inventions or increased prices paid for end-products relative to non-patented alternatives. While there is no conclusive evidence that patents have undesirably influenced research direction (particularly given the research exemption that exists), the property rights embedded in a patent could lead to this outcome and there are anecdotal claims that this has been the case.

By and large, the risks of an isolated human gene sequence patents relate to the terms and conditions of access to patented inventions, and the lost or reduced opportunity for market competition to drive efficiency and quality control.

Key threshold questions likely to influence whether patents may deliver net value or net costs include:

- the extent to which patents matter to incentivising upstream human genetics research;
- the extent to which patents matter to technology transfer between upstream and downstream researchers;
- whether upstream isolated human gene patents are critical to the entry of candidates to clinical trials, particularly where private investment is required;
- the extent to which isolated human gene sequence patents are critical in achieving a positive rate of return on R&D;
- whether access to upstream human genetic technology is available under licence or by other arrangements during the patent term;
- whether the cost of access, or conditions of access, to patented technologies is excessively onerous; and
- what the patented technology is useful for — costs are likely to be less significant (or more easily justified) when research relates to the development of similar products, compared to follow-on uses to develop different but competing products, or useful for developing non-competing follow on uses.

Stocktake of isolated human gene patenting in Australia

The number of isolated human gene patent applications has steadily reduced since the Human Genome Project, with a discernible trend towards method (use) only patents and patents that do not have a counterpart in nature.

New research on isolated human gene patents in Australia show that isolated human gene patenting activity is changing. Today there is a strong focus on method-only patents, and isolated human gene sequence patents that do not have a counterpart in nature.

There is no transparent recording system in Australia than enables the ready identification of isolated human gene patents. Based on a patent search strategy designed to target the primary areas of focus for human genetics research, there are at least 3000 to 4400 patent applications (with 95 per cent confidence) that include at least one claim to an isolated human gene sequence that have ever been filed in Australia.

The Human Genome Project (HGP) and its successors have had a significant effect on isolated human gene patent applications, resulting in a sharp reduction in the overall number of isolated human gene patents being granted.

The vast majority of full-length isolated human gene sequence patent applications were filed prior to the completion of the HGP in 2003.

Based on the sampling undertaken for this study, approximately 37 per cent of all patents relating to isolated human gene patents granted in Australia are still in force. In terms of

actual patents granted, there is estimated to be 456 (and most likely between 284 and 627[1]) isolated human gene patents *in force* in Australia today which claim some aspect of an isolated human gene, that fit within the definition of an isolated human gene patent used for this study. Only 4.8 per cent of isolated human gene patents are estimated to be held by Australian entities.

Of those in force today, 57 per cent *do not* have a counterpart in nature (that is, they are patents for which there is no identical DNA molecule in the human body). Of those that are in force, 60 per cent are for partial length gene sequence patents. Most granted patents that have a counterpart in nature (74 per cent) are no longer in force (having expired or ceased). The reduction in patents over isolated human gene patents is occurring at a time when gross business expenditure on R&D in the medical and health sciences sector has tripled over the past 10 years, and NHMRC funding for research on human genetics and genomics issues for largely public entities has increased by two and half times.

1 Data on the 'most likely' number of patents reflects statistical analysis on the sample and the reporting of results at the 95 per cent statistical confidence interval.

1 What is an isolated human gene patent?

There are varying views on the merits of isolated human gene sequence patents. Where proponents claim that patents are crucial to supporting high risk and high cost medical discovery and development, critics are concerned about how they might limit the accessibility and inflate the price of healthcare and diagnostic services.

Isolated human gene sequence patents are the subset of total isolated gene sequence patents, which include at least one claim to an isolated human gene sequence. Definitions of patentable human genetic technologies change over time, coinciding with the rapid progress of scientific discovery.

Understanding the controversy

There is ongoing debate on the merits of isolated human gene patents, and of what is, or should be, a legitimate and appropriate definition of an isolated human gene patent.

In some cases, concerns reflect a misunderstanding about what is patentable and what patenting allows or prohibits. There are also genuine differences in perspective from legal and medical professionals on these issues, and uncertainty created by changes that occur over time as to what meets the criteria for patentable subject matter.

The key concerns about isolated human gene patents are highlighted in box 1.1.

The definition of a 'patent' is reasonably straightforward, with clearly set parameters for patentability of an invention. The intent is to strike an economic trade-off by granting a temporary monopoly over a product or method that would otherwise not be developed without the granted period of exclusivity when large research and development (R&D) costs can be recouped and profits obtained.

Defining an 'isolated human gene' patent can be more controversial, given the fast paced development and change in medical research relating to isolated gene sequences and new applications and uses of genetic information.

Rapidly changing technologies present a challenge to patent regulatory authorities who need to keep abreast of new developments and techniques (and notions of inventiveness and usefulness). Patent holders may need to defend awarded patents over the life of the patent.

This report does not comment on the legal or medical opinion that defines an isolated human gene patent. An isolated human gene patent is defined in accordance with the existing regulatory framework, and demonstrated by the type and nature of isolated human gene patents that have been approved in Australia.

1.1 Key concerns surrounding isolated human gene patents

The key concerns voiced by various stakeholders about isolated human gene patents can be summarised as follows.

- Materials isolated from nature should not be patentable, and should be freely available to all, for research and application purposes.
- The existence of a patent covering an isolated biological material might inhibit the course of research and thereby deprive society of new knowledge or future medical advances.
- The availability of important medical treatments or diagnostic tools might be too expensive and/or not widely available because of a patent, thereby depriving individuals of the best care.
- There is a perception that, without patents, there would be more competition between diagnostic, biopharmaceutical and biotechnology companies, which would provide wider and less expensive access to new diagnostics and drugs.
- There is a belief that the genes of individuals might be patented and therefore 'owned' by someone other than the individual.
- There is a concern that the threshold of inventiveness is too low, allowing patents to be granted that are undesirable, unethical or offensive.
- These concerns have been voiced in a number of submissions to the Senate Community Affairs Committee Inquiry into Gene Patents, such as the Breast Cancer Network Australia and Cancer Council Australia. The Cancer Council Australia also suggested that, should the question of isolated human gene patents not be resolved within five to ten years, that open licences be introduced for genes and genetic testing.

Source: Selected submissions to the Senate Community Affairs Committee Inquiry into Gene Patents, which tabled its report in November 2010.

Purpose of this review

The purpose of this review is to analyse evidence on the economic costs and benefits to Australia of the patenting of isolated human genes.

This report is intended to fill key gaps in the existing literature to focus specifically on:

- the economic impact of isolated human gene patents — their impact on incentives and disincentives to undertake research and to commercialise research; and
- providing evidentiary support to issues associated with the impact of isolated human gene patents, including the order of magnitude associated with different impacts (both positive and negative).

It is not the intention or purpose of this report to make any value judgements about the patenting of isolated human genes or to draw any policy implications.

Rather this report provides information on some of the 'missing pieces' in the understanding of isolated human gene patents to provide policymakers and other stakeholders with a more fulsome understanding of the issues, and to complement other pieces of work on important medical, scientific, legal and ethical matters associated with isolated human gene patents.

Areas of scope of this report

The themes for this review are set out below.

1 ***Understanding the financial arrangements associated with isolated human gene patents in Australia*** for Australian entities, including research entities, which own or have owned gene patents claiming isolated human gene sequences. This includes income received, access to investor finance, international collaboration and research funding.

2 ***The role of patents in the business of bringing new medicines and diagnostics to market.***

3 ***The economic value to Australia of the patent incentive*** for gene patents claiming isolated human gene sequences. This includes any spillover effects and access to new technologies and treatments, both from the direct patent incentive and from follow-on innovations.

4 ***Costs to Australian consumers and society*** as a result of paying higher prices for isolated human gene sequence innovations resulting from higher prices for patented products in the absence of competition, flow-on costs from negotiating access to patented genetic sequences, flow-on costs from patent validity and infringement disputes, and costs to society as a result of the disincentive for follow-on innovation and for the introduction of new treatments and methods of diagnosis, due to the costs and barriers of negotiating licences for the use of patented isolated human gene sequences.

5 ***First inventions*** relating to an isolated human gene sequence to market ***compared to follow-on inventions.***

6 ***A stocktake of isolated human gene patents in Australia.***

Evaluation method

The key methodological steps involved in this review include the following.

- Literature review — an extensive review of the literature on the economics of patents and issues associated with isolated human gene patents has been undertaken to understand the debate in the scientific literature on the evidence and impact of isolated human gene patents.
- Stakeholder consultation — numerous face-to-face meetings and some telephone interviews were held with key stakeholders, including the funders of research and downstream products (medicines and diagnostics), research entities, pharmaceutical companies, biotechnology companies, diagnostic laboratories and their respective associations, public hospitals, academics, intellectual property rights (IPR) lawyers,

clinicians, relevant societies and key individuals that were able to provide comment and evidence on the breadth of issues for this review.

- Analysis of the AusPat patent database to undertake a stocktake of isolated human gene patenting activity in Australia and analyse characteristics of isolated human gene patents, including changes over time.
- Collection of data on the economic activity of entities involved in the area affected by isolated human gene patents, as well as volume and pricing data related to relevant downstream products, and financial transactions associated in some way with isolated human gene patents.
- Quantitative analysis to estimate the direct impacts of isolated human gene patents.
- Qualitative analysis to draw on the indirect impacts of isolated human gene patents.

Defining a patent

A patent is a document issued upon allocation by a government agency which 'describes an invention and creates a legal situation in which the patented invention can normally only be exploited (manufactured, used, sold, imported) with the authorisation of the owner of the patent'.[2]

Broadly, countries provide laws to protect intellectual property for two main reasons:

- to give statutory expression to the moral and economic rights of creators in their creations and the rights of the public in access to those creations; and
- to promote, as a deliberate act of government policy, creativity and the dissemination and application of its results and to encourage fair-trading which would contribute to economic and social development.[3]

Requirements for the patentability of an invention

The legislation that governs the patent system in Australia is the *Patents Act 1990*. The Act stipulates a number of threshold criteria for the patentability of an invention. For instance, the Act provides that an invention will be patentable if, inter alia, it:

- is a **'manner of manufacture'** — a patent must relate to an artificial state of affairs. That is, a product, process or method that arises through some form of 'human intervention with nature to bring about some physical change';[4]
- is **novel** — a claimed invention must not be previously known in a given field of knowledge. This means that details of the invention must not have been 'published or made publicly available through use anywhere in the world';[5]

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2 The World Intellectual Property Organisation 2004, *Intellectual Property Handbook: Policy, Law and Use,* Second edition, Geneva, p. 17.

3 Ibid, p.3.

4 Davison, M. Monotti, A. Wiseman, L. 2008, *Australian intellectual property law*, Cambridge University Press, Melbourne, p. 377.

5 ibid.

- involves an **inventive step** — whether an invention involves an inventive step is judged by a comparison with the state of knowledge in the field relevant to the invention, which is referred to as the 'prior art base';
- is **useful** — which is satisfied only where a patent application discloses a 'specific, substantial and credible' use[6]; and
- the **details** of the invention are sufficiently **well disclosed or described**.

The legal principals of what is eligible for patent protection in Australia was established in 1959 in the landmark decision from *National Research Development Corporation v The Commissioner of Patents* (the NRDC case).[7] In this case, the High Court indicated that a policy-oriented approach should be adopted establishing relevant criteria of patentability.

For an invention to be a 'manner of manufacture', as interpreted in NRDC, it must belong to the 'useful arts' rather than the 'fine arts', it must provide a material advantage, and its value to the country must be in the field of economic endeavour. The judicial interpretation also recognised a number of categories of subject matter that fail to satisfy the test — including mere discoveries, ideas, scientific theories and laws of nature.

This judicial interpretation and the lack of express prohibitions on patentability in the Act have had an expansive effect on patentable subject matter in Australia, and the categories of inventions that satisfy the manner of manufacture test have gradually expanded over time.[8]

The recent Federal Court decision in *Cancer Voices Australia v Myriad Genetics Inc. [2013] FCA 65* concluded that isolating naturally occurring DNA (Deoxyribonucleic Acid) or RNA (Ribonucleic Acid) created 'an artificially created state of affairs', and consequently was able to be patented. His Honour arrived at this conclusion after considering the:

- 'broad sweep' interpretation given to 'manner of manufacture' in the National Research Development Corporation case;
- difference between 'isolated' and naturally occurring nucleic acid; and
- purpose of the Patents Act in rewarding the skill and effort of inventors.[9]

The decision has been appealed to the full bench of the Federal Court.

The regulatory framework governing isolated human gene patents is also affected by international agreements including the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which have placed additional requirements on patentability. For instance, TRIPs provides that patent rights shall be applied equally

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6 Intellectual Property Laws Amendment (Raising the Bar) Act 2012.

7 National Research Development Corp v Commissioner of Patents (1959) 102 CLR 252. The patent at issue claimed a novel treatment for killing weeds in crops. The question before the High Court was whether agricultural and horticultural inventions were patentable under Australian law.

8 Australian Law Reform Commission 2004, *Genes and ingenuity: gene patenting and human health*, June, p. 118.

9 DLA Piper 2013, *Australia: Federal Court hands down decision of Cancer Voices Australia v Myriad Genetics Inc: Life Sciences Alert*, February.

'without discrimination as to the field of technology'. This dimension of 'technological neutrality' is important to an impact assessment of isolated human gene patents, as the alternative case of 'no patents', or altered patent rules for isolated human gene patents only, would need to consider the impact of treating isolated human gene patents different to other forms of technology.

Defining what is, and what isn't an isolated human gene patent

An 'isolated human gene patent' for the purpose of this study is a patent that includes one or more claims over an isolated or purified genetic sequence that can be found in humans, which could be a claim to:

- an isolated human full length gene sequence (that is, an isolated gene sequence encoding a human protein);
- an isolated human partial gene sequence (that is, a sequence that corresponds to only a portion or fragment of a full length gene such as a probe or primer sequence); or
- a modified isolated human gene sequence (that is, a sequence that has been altered in some way from its naturally occurring counterpart, such as a sequence altered to code for an altered protein with improved properties from the wildtype).

Individual researchers and entities are able to make a claim for some aspect of an isolated human gene if they are able to satisfy patentability criteria in the *Patents Act 1990*.

The purpose of patenting is it to exclude others from making, using or selling the product or process defined by the patents claims unless agreed to by the patent holder. Anyone else seeking to do these things for purposes *other than research* will require permission of the patentee.[10]

Patent applications comprise a set of claims that set out the scope or limits of what is protected by the patent. A patent for isolated human genes and genetic material may comprise product claims (either full or partial isolated human gene sequences), a process claim for making a product, or a method claim of making or using a product.[11] Claim types typically found in isolated human gene patents are shown in table 1.2.

Key categories that *are not* considered isolated human gene patents for the purpose of this study include:

- patents that claim a protein sequence, but do not claim any genetic/DNA sequence;
- a microarray, this is a tool that uses a very specific set of probes for genetic testing;
- an invention that describes a method of genetic engineering (that is, expression systems); and
- inventions that claim the genetic sequence of only non-human organisms such as other mammals, other animals, plants and micro-organisms such as viruses and bacteria.[12]

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10 Research exemptions exist for isolated human gene patents as discussed further below.

11 IP Australia/DIISR, Senate Committee Community Affairs: Inquiry into Gene Patents, p.6.

12 Holman, M, C, 'Debunking the myth that whole-genome sequencing infringes thousands of gene patents', 2010, *Nature Biotechnology*, Vol 30, No. 3, pp. 240–244.

1.2 Claim inclusions

Type of claim	Description
Product claim	Typical product claims include: ▪ an isolated gene sequence *per se*; ▪ an isolated protein encoded by the isolated gene sequence; ▪ vectors harbouring the isolated gene sequence; ▪ cell lines transformed with the vectors or sequence; ▪ recombinant protein expressed from the cell lines; Other products related to what the isolated gene sequence could be used for. For example, antibodies and vaccines, which can be used to treat diseases: ▪ antibodies produced using the isolated sequence or fragments of the sequence; ▪ vaccines and compositions comprising the isolated sequence or protein; ▪ probes comprising the isolated sequences or fragments; and ▪ kits comprising the sequence or specific primers or fragments of the sequence.
Method claim	Method of using an isolated gene sequence for diagnostic and therapeutic purposes. **Therapeutic:** ▪ a gene therapy and/or using the protein encoded by the isolated gene as a therapeutic to treat a disease or disorder associated with the gene; and ▪ methods of identifying molecules that modulate or interact with the gene wherein the methods are directly based on the use of the isolated sequence. **Diagnostic:** ▪ use of an isolated gene or protein sequence to diagnose/prognose disease or disorders associated with the gene.

Source: IP Australia/DIISR, Senate Committee Community Affairs: Inquiry into Gene Patents, Chapter 4.8 and 4.9, 2010.

A never ending story: changes in research, patents and products

Medical research is a rapidly growing and changing environment. What is 'novel', 'useful', patentable, and desirable continues to change as more becomes known about medical conditions and disease patterns.

Chart 1.3 sets out the key phases in human genetic research over time, and key isolated human gene patents that illustrate patenting activity at the time.

This highlights one of the challenges for cutting-edge areas of research, such as human genetics, given that patents provide intellectual property rights (IPR) protection for a duration throughout which new knowledge is changing and concepts of inventiveness are being redefined.

Evolution in medical science and implications for patentable human genetic research

Over the last several decades, there has been an increase in human genetics research in Australia (see chapter 2), and considerable patenting activity claiming a full or partial isolated human gene sequence and/or therapeutic or diagnostic uses of a full or partial isolated human gene sequence (see chapter 3).

The beginning of academic interest

Human genetics research is understood to have begun in 1966, with published scientific references on carrying out human gene therapy by Edward Tatum and Joshua Lederberg.

At a symposium titled 'Reflections on Research and the Future of Medicine' at Columbia University College of Physicians and Surgeons in New York City in 1966, Tatum spoke optimistically about the long-range possibility of therapy based on the isolation or design, synthesis, and introduction of new genes into defective cells of particular organs.

In the September–October 1966 issue of The American Naturalist, Lederberg addresses the concept of engineering human cells in an article entitled 'Experimental Genetics and Human Evolution'.

The first isolation of a gene, by Jonathan Beckwith and his colleagues at Harvard, was described in an article on the front page of the *New York Times* (November 23, 1969). Concerns about the potential misuse of human genetic engineering were also arising, reflected in books written with explosive titles such as *The Biological Time Bomb*, by Gordon Rattray Taylor (1968), and *The Second Genesis. The Coming Control of Life*, by Albert Rosenfeld (1969).[13]

In the early to mid-1970s methods for reading DNA sequences began to emerge and researchers successfully developed molecular cloning. Biotechnology companies start to form with early success in manufacturing human protein.

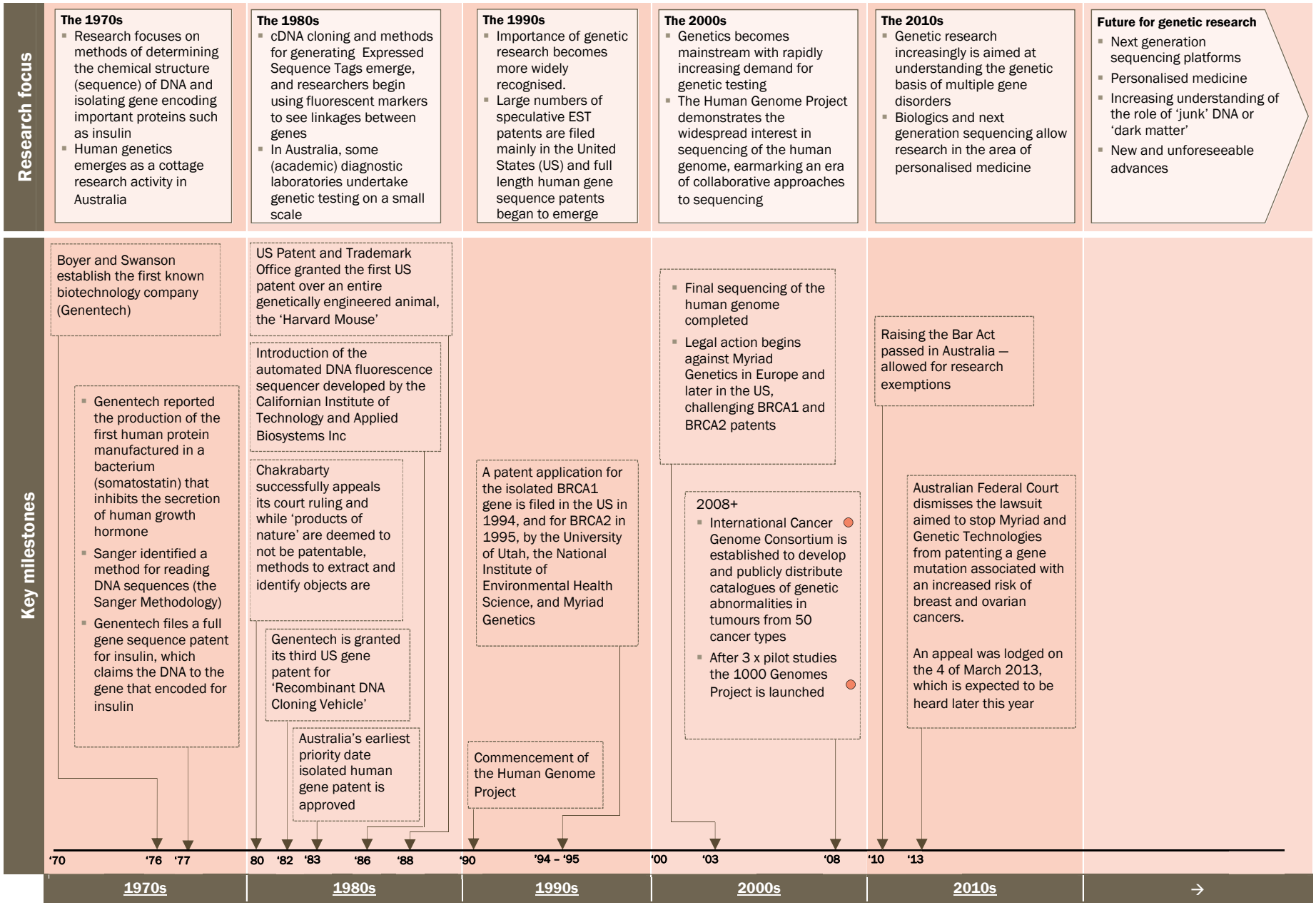
Various patents were approved for the isolation of whole genes that were associated with a protein (or for artificially generating genetic information in a laboratory, which is known to occur in humans). The most commonly cited (and controversial) example was the patent for insulin acquired by Genentech (Genetic Engineering Technologies).

In Australia in the 1970s, human genetic research was a 'cottage' area of research, undertaken by academic researchers that were exploring a new frontier in medical science.

Human genetic research continued to evolve throughout the 1980s, although it was yet to become mainstream. In 1983, Australia's earliest priority date isolated human gene patent was approved, which was a patent for molecular cloning and characterisation of the isolated gene sequence coding for human relaxin. Some diagnostic laboratories in Australia were undertaking small-scale genetic tests, although it is understood from stakeholder consultations that this was limited to laboratories staffed by formerly academic researchers.

13 Anderson, W. F., 'Human Gene Therapy: The Initial Concepts', University of Southern California School of Medicine Los Angeles, California http://cmbi.bjmu.edu.cn/cmbidata/therapy/about/PDF/pre1980.pdf, Accessed 14/02/12.

1.3 Evolution of human gene research and the protection and dissemination of information



Source: The CIE, ALRC (XXXX) Genes and Ingenuity: Gene patenting and human health, ALRC report 99/3.

A wave of speculative patents without a counterpart in nature

In the 1980s, Expressed Sequence Tags (ESTs) were becoming a focus of research, a process of making cDNA (complementary DNA) from copies of mRNA and selecting these clones from a cDNA library for sequencing. These ESTs were connected to fluorescent markers and used to see linkages between genes.

In 1992, the National Institutes of Health (NIH) applied for two patents in the United States (US) covering 2715 genes, which were sequences of the ESTs. The patent applications were withdrawn in 1994 in response to concerns that the emerging biotechnology sector would be harmed. Since then biotechnology companies have now applied for patents covering hundreds of thousands of ESTs.[14] These patents cover a short sub-sequence of an isolated human gene and have no counterpart in nature.

Full length human gene sequencing emerges

By the 1990s, the importance of human genetic research became more widely recognised, and full-length isolated human gene sequence patents began to emerge — the most well-known being BRCA1 (breast cancer susceptibility gene 1) and BRAC2 (breast cancer susceptibility gene 2) (see box 1.4).

Collaborative approaches to human genetics research become established in areas of basic as well as commercial research

In 1989, the Human Genome Project (HGP) commenced, which changed the playing field for what was considered novel findings in human genetic research. It also precipitated a drift in patenting activity from the sequence of a human gene or encoded protein to its uses (discussed further in chapter 3).

The HGP is an international scientific program that aimed to identify and map the entire human genome. It is now run by the National Human Genome Research Institute (NHGRI) and was established by the National Institute of Health (NIH) in the United States. A draft of the HGP was published in 2001 and a complete version in April 2003. The main goal of the project was to identify all 30 000 genes in human DNA and although the database is published, analysis of the data is ongoing.

The major impact the HGP had on patents is that information surrounding the human genome and processes of genetic sequencing were made publicly available and widely known. Patent applications after the final publication of the HGP in 2003 needed to satisfy the novelty requirements in light of the new information.

14 Pieroni, J., The Patentability of Expressed Sequence Tags, http://www.fitzpatrickcella.com/DB6EDC/assets/files/News/attachment148.pdf.

1.4 Overview of the patenting of BRCA

Following sixteen years of publicly funded research, in 1990 researchers at the University of California San Francisco discovered that hereditary breast and ovarian cancers were linked to a gene on human chromosome 17. This was licensed to a US company OncorMed.

The University of Utah's Centre for Genetic Epidemiology formed a spin-off company Myriad Genetics Inc. in 1991 (which acquired OncorMed) after compiling a database of mutations in patients. Myriad used this database to leverage funding from Eli Lilly despite at this stage not owning any patents. Myriad was formed to identify the gene on human chromosome 17 that was linked to breast and ovarian cancer and then patenting the isolated gene to control the genetic diagnosis of these cancers. Myriad identified and termed the breast and ovarian cancer susceptibility gene on chromosome 17 'BRCA 1'.

The following patents were granted, US 5 693 473 'BRCA1' held by Myriad, le Centre de recherché du CHUL, Quebec, Canada, and the Cancer Institute in Tokyo, Japan. Other patents relating to the BRCA1 and the associated diagnostic tests US 5 709 999; US 5 747 282; US 5 710 001; US 5 753 441; and US 6 162 897.

Further research identified 'BRCA 2' as a second breast cancer susceptibility gene on human chromosome 13. Myriad filed a patent application claiming BRCA2 DNA, mutations, and diagnosis on April 29, 1996, and for a patent over the method of detecting BRCA2 mutations and antibodies on March 20, 1998. The USPTO granted these patents on November 17, 1998 (US 5 837 492) and September 26, 2000 (US 6 124 104) respectively.

BRCA1 and BRAC2 tests were performed by Myriad Genetics, and its subsidiary, Myriad Genetic Laboratories, Inc. ('Myriad'). By the late 1990s, Myriad had licensed 13 laboratories its diagnostic test. In Australia in 2002 Genetics Technologies Ltd (GTG), a publicly listed Australian company headquartered in Melbourne, negotiated an exclusive license from Myriad to all BRCA1 and BRCA2 patents (there are four in total) that had been granted to Myriad and various other organisations (in respect of two such patents, the US Department of Health being one of the patentees).

Litigation over the BRCA patents held by Myriad is ongoing internationally concerning the patentability of diagnostic tests and to what extent a diagnostic test represents an innovative application of a rule of nature.[15] However, in February 2013 the Federal Court determined that a valid patent may be granted for a claim that covers naturally occurring DNA or RNA that has been 'isolated' (extracted from cells obtained from the human body and purged of other biological materials with which they were associated). The decision was based on the finding that isolating nucleic acid constituted 'an artificially created state of affairs'.[16]

15 Abbott, A. 2008, Europe to pay royalties for cancer gene: BRCA1 patent decision may be ignored in clinics, Nature, December 456, 556.

16 *Cancer Voices Australia v Myriad Genetics Inc* (2013) FCA 65.

Following the HGP other collaborative partnerships were formed, demonstrating a growing tendency towards collegiate interaction and cross-institutional cooperation in the field of human genetic research.

- The International Cancer Genome Consortium (ICGC) was established to coordinate the generation of comprehensive catalogues of genomic abnormalities, and lead to a centralised, publicly available information resource to facilitate and expedite international research on cancer. Its primary goals are to generate comprehensive catalogues of genomic abnormalities (somatic mutations, abnormal expression of genes, epigenetic modifications) in tumours from 50 different cancer types and/or subtypes which are of clinical and societal importance across the globe. This data is to be made available to the entire research community with minimal restrictions to accelerate research into the causes and control of cancer. Australia has contributed $27.5 million to the ICGC via the NHMRC.[17]
- The 1000 Genomes Project launched in 2008 was established to produce an extensive public catalogue of human genetic variation. It has sequenced the genomes of a large number of people to provide a comprehensive resource on human genetic variation available to the worldwide scientific community through freely accessible public databases.[18]
- Global biotechnology and biopharmaceutical companies are also, at times, taking a collaborative approach to R&D. For instance, Boehringer Ingelheim undertakes some collaboration with other companies and universities in the development of biopharmaceuticals, when there is 'no time for rivalry' and companies enter into strategic co-operations when licensing the product.[19]

Modern genetic research

Modern genetic research often does not cover just one gene and one disease, but families of genes and in relation to a disease state. These sorts of inventions can still be patentable, and can lead to better targeting and personalised medicine. For instance:

- next generation sequencing allows large stretches of DNA pairs spanning entire genomes to be rapidly sequenced. The process has generated a sea change in genetic research, providing major leaps forward on understanding and accessibility of research into the genome, transcriptome and epigenome;[20]
- biologics (a class of therapeutics utilising recombinant DNA technology) are being tailored for individuals with vast curative potential — the main current applications are for rheumatology and oncology, but research is expanding this field to include cardiology, dermatology, gastroenterology and neurology;
- monoclonal antibodies are being used to fight off bacteria and viruses, which are 'custom-designed' (using hybridoma technology or other methods) and can be made

17 NHMRC 2010, 2010–2012 Strategic Plan, Commonwealth of Australia, Canberra.

18 http://www.1000genomes.org/about.

19 Jungbauer, A., U., Göbel BTJ Forum, Biopharmaceutical process development — shortcut to market: an interview with Rolf Werner from Boehringer Ingelheim, *Biotechnology Journal*, 2012 Volume 7, 14–16.

20 Illumina (n.d.) An introduction to Next-Generation Sequencing Technology.

specifically to counteract or block any given substance in the body, or to target any specific cell type.

Patent law and tests for patentability have also coincided with progress in scientific discoveries when claimants and competitors vie for market position and seek to shape the nature of isolated human gene patents (see appendix A).

Exemptions for research

On 15 April, 2012 the Australian Commonwealth *Intellectual Property Laws Amendment (Raising the Bar) Act 2012* (Cth) (*Raising the Bar Act*) received Royal Assent, which introduced, among other things, an exemption from patent infringement for experimental activities to give researchers 'greater certainty about where they have freedom to operate around patented technology'. The exemption came into force on 16 April, 2012 exempting experimental activities done on or after that date.

This followed a lengthy review of Australian IP legislation in the years to 2012, which included a number of Commonwealth Government commissioned reports, Senate investigations and extensive consultations around a proposed, and then enacted, *Intellectual Property Laws Amendment (Raising the Bar) Act 2012.* Leading up to the *Raising the Bar Act* being passed, the Australian Government response to the Senate Committee Gene Patents Report (2011) accepted a number of broad ranging principles, which paved the way for a review of the legislation.

The experimental use exemption included in the new Act, makes it clear that exemptions to the use of patent material are made for experimental purposes of:

- determining the properties of the invention;
- determining the scope of a claim relating to the invention;
- improving or modifying the invention;
- determining the validity of a patent or of a claim relating to the invention; and
- determining whether the patent for the invention would be, or has been, infringed by the doing of an act.

The *Raising the Bar Act* also introduced a specific, substantial and credible use criteria, going beyond the previous requirement of identifying the invention as 'useful'. It also removed reference to Australia when measuring inventiveness based on the general knowledge in the art, and removed the prior art requirement of 'information that a skilled person… could… have ascertained, understood and regarded as relevant'.[21]

Why patent? Understanding the economic objective of patents

Intellectual property rights seek to promote economic development by providing an incentive for inventors to create and disclose their work. In this sense, the goal of the patent system is 'fundamentally economic'. The patent system seeks to:

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21 Swinn, M. (2012) So Australia has raised the bar in IP… What do I need to know? http://www.corrs.com.au.

- encourage the availability of new and useful technologies to society through the incentive of legally enforceable exclusive rights to commercially exploit any device, substance, method or process that is new, inventive, and useful for the life of the patent. In the case of pharmaceutical innovations, rights exist for 20 years;[22] and
- promote innovation through encouraging the diffusion of knowledge.

These objectives are particularly relevant in the medical research environment — which is highly uncertain — requiring many years of research (typically 12–15 years) without a guarantee of success and billions of dollars to be invested to develop new technologies to a marketable standard.[23]

Achieving the objectives of patents could be done via Common Law Protection for Trade Secrets, however, this would be more restrictive and less competitive ways, and would forego disclosure of the innovation and result in duplicative research and/or deny opportunities for work-around innovations to be spurred.

The economic importance of patents is readily observable in practice. For instance, every product brought to market by CSL Ltd, Australia's largest biotechnology company with a market capitalisation of $23.2 billion in 2012 is the subject of a patent. Merck Sharp and Dohme (Australia) Pty Ltd noted that without the protection of a strong system and enforcement regime, MSD would not be able to invest in Australia — licensees of Merck products supply vaccines including GARDASIL and MMR II.[24]

The protection of pharmaceutical inventions also covers issues such as data protection, which is vital for the pharmaceutical and biotechnology sector as noted by Novartis:

> the current 5-year data exclusivity for new molecular entities is an absolute minimum in order to protect the considerable investment originators make into generating the data to show the effectiveness and safety of new drugs.[25]

The economics of bringing isolated human gene based products to market and the role of patents is discussed further in chapter 4.

The economic rationale behind intellectual property

Intellectual property differs from normal physical property in that it is based solely on information. As such, if one person is using intellectual property it will not prevent or diminish simultaneous use of that intellectual property by another person.[26]

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22 The length of a patent term extension can be up to five years, but has to be applied for after the first regulatory approval. A patent term extension will not be granted if the period between the date of the standard patent and the date of the first regulatory approval of the pharmaceutical substance is less than five years. The intention is to provide up to 15 years of 'effective' patent term from regulatory approval to patent expiry. Griffith Hack, Pharmaceutical Patent Term Extension in Australia, available at: http://www.griffithhack.com.au/Assets/1529/1/GH6088PharmaPatentTermExtensions.PDF.

23 Medicines Australia, 2013. Submission to Australian Government Pharmaceutical Patents Review.

24 MSD, 2013. Submission to the Pharmaceutical Patents Review Panel.

25 Novartis Pharmaceuticals Australia Pty Ltd, 2013. Submission to the Australian Government's Pharmaceutical Patents Review.

Without legal intervention, economically valuable intellectual property can be freely appropriated or copied by other parties, without compensation to the innovator. This gives rise to what is described as a 'free rider' problem by second comers,[27] which erodes incentives to innovate and makes firms less willing to incur the substantial up-front costs of investing in research and commercialisation activities.

Hence, it is more efficient in the long-term to provide defined property rights in information to ensure that incentives remain to invest in new information.

These characteristics of information create a fundamental economic trade-off.

> An overly protective system of IPRs could limit the social gains from invention by reducing incentives to disseminate its fruits. However, an excessively weak system could reduce innovation by failing to provide an adequate return on investment.[28]

Economic theory promotes 'public intervention to stimulate invention in cases where ex-post competition would reduce the market price to a competitive level and deter ex-ante costly investment'.[29]

In this case, intervention will encourage new business development and induce new technology acquisition and creation.[30]

In practice, there is a degree of uncertainty surrounding the competitive structure of markets, and the efficiency of IPR and other regulatory arrangements that impact on entities involved in human genetic research and downstream commercialisation.

For this reason, IPRs will never be able to 'make a perfect market', but they are important, and in many cases essential, to provide second best remedies for underlying market distortions.

Do patents create monopolies?

It is commonly argued, that patents create a 'temporary monopoly', given that they confer an exclusive right over the patented invention for a specified period. Patent rights provide the patentee with market power — allowing a firm to raise the price of a patented product above the normal equilibrium price and not lose market share to competitors.[31]

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26 Economists describe this as their being no marginal cost to the use of existing knowledge.

27 Free riding becomes an economic problem where it is not possible to exclude others from consuming or benefiting from actions or goods. Where exclusion is not possible, it is difficult to require payment and return for use, which in turn reduces the final value of the product or service to its creator, reducing the initial incentive to create and face costs of establishment and production. The ultimate effect is that less goods and services are produced or offered than would be efficiently provided in a market where creators were able to retain market returns.

28 Maskus, K. 2000, *Intellectual Property Rights and Economic Development*, February.

29 Peterson Institute for International Economics 2000, *Intellectual Property Rights in the Global Economy*, August, p. 29.

30 The licensing arrangements of patented technologies are likely to be a key determinant of the economic consequences of patented material. The use of closed, restrictive or exclusive licensing models is likely to heighten potential risks to the accessibility, affordability, accuracy and timeliness of genetic testing services.

31 In the absence of patents rights, competition would force the price at which an invention can be sold to the marginal cost of production.

However, while patents provide the exclusive right to control access to an asset — a *property monopoly* — they seldom provide the patentee with complete *economic monopoly* power over the market. In most cases, there will be technical and economic substitutes for the invention that will serve as competitors for the patentee, thus limiting the scope of any economic monopoly. That is, while the patent prevents competitors from using the specific patented invention, it does not prevent competitors from using substitute products or services to capture market share.[32]

> it is a confusion to call patents and copyrights 'monopolies,' because… a monopoly is a good supplied by a single supplier that has no close substitutes in use. Thus, a patent or copyright may confer monopoly pricing power — but so may a property right in something tangible, such as a strategically located parcel of land. Moreover, a patent or copyright confers no monopoly where there are satisfactory substitutes for the new invention or writing.[33]

Further, distinct from monopolies which aim to restrict output and competition, patents aim to promote output through innovation by permitting a reward for effort.[34]

> … both intellectual' and 'tangible' property rights may lead to monopoly, but the purpose (and general effect) of those rights is to promote rather than to restrict competition and economic output.[35]

The relationship between patents and innovation is shown in chart 1.5. In an effort to improve profits, firms innovate to lower production costs and/or improve and differentiate their output. Patentability over this 'new' product allows the firm to receive a reward for their effort. However, higher profits incentivise rival firms to 'design around' the raw product and innovate themselves in order to compete in the marketplace. Once these competitors are successful, they reduce the profitability of the original firm, which in turn, spurs a new round of innovation.

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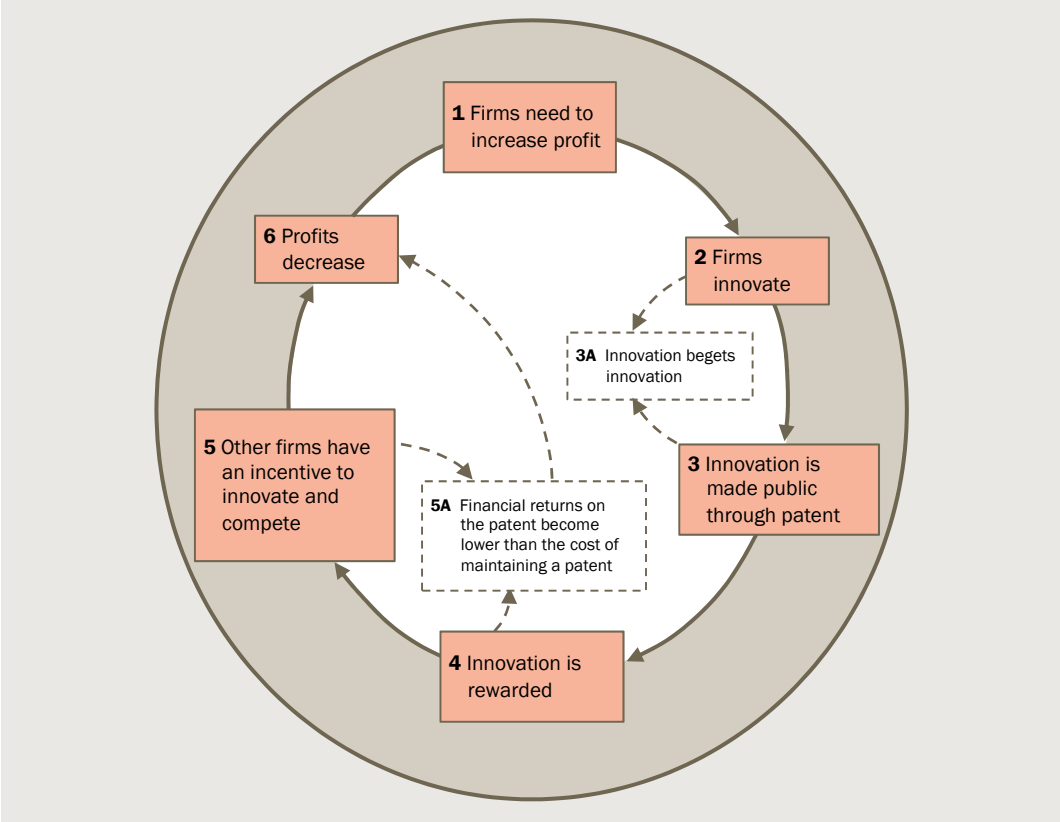
32 Murphy, W. Orcutt, J. Remus, P. 2012, *Patent valuation: Improving Decision Making through Analysis*, Wiley Finance, p.108.

33 Novak, M. 1996, *The Fire of Invention, the Fuel of Interest: on Intellectual Property*, The AEI Press, Washington DC.

34 The CIE 1999, *Intellectual Property Rights in Agricultural Trade*, prepared for the World Bank's Integrated Program of Research and Capacity Building to enhance participation of developing countries in the WTO 2000 Negotiations, October, Geneva.

35 Novak, M. 1996, *The Fire of Invention, the Fuel of Interest: on Intellectual Property*, The AEI Press, Washington DC.

1.5 Source of value from the patents that create a market for innovation



Source: The CIE.

How does this apply to isolated human gene patents?

An isolated human gene patent provides the inventor with the exclusive right to make, use and sell the invention. The life of an isolated human gene patent is up to 20 years, after this other firms are able to use this invention freely. The protection given to inventors is defined by the claims granted, hence it is the claims that determine the restrictiveness of the patent. In some cases, other firms are able to utilise a patented technology if a license or permission is sought from the inventor.

Incentives to innovate, irrespective of the patent regime, are strong in the human genetics area with the potential for discoveries to directly improve health outcomes. Medical advancement is based on the changes in existing knowledge and technology from previous innovations.

In many cases, particularly for biotechnology companies, the patent is a tool — not for a monopoly right, but is essential to secure capital investment from other firms to enable research to continue. In some cases, the company succeeds and there is a new diagnostic or therapeutic on the market, but in most cases the invention fails and the firms must again innovate. The limited life span on the patent for the product, along with the other drivers, is intended to incentivise the next round of innovation.

Hence, while no monopoly is ever achieved, the patent has helped expand medical knowledge and advancement. The direct and indirect financial and non-financial values of isolated human gene patents are explored further in chapter 5.

Common gene patent misconceptions

There are several misconceptions about isolated human gene patents that, to a certain extent, perpetuate some of the controversy about isolated human gene patents. The two most commonly referred to are:

- patents are held over as much as 20 per cent of human genes; and
- that an isolated human gene patent grants ownership over the physical material of any person.

Strictly speaking, it is not known precisely what proportion of the human genome is subject to isolated human gene patents. There is a widely held belief that 20 per cent of human genome sequence is patented in the United States.[36] This notion is based on a 2005 paper by two American scholars Jensen and Murray, who attempted to provide a landscape of the patents over isolated human genes. Their dataset of isolated human gene patents was created by searching for patents using the search term 'SEQ ID NO' (which is now a term required by the USPTO in filings over claims related to a genetic sequence). The authors linked isolated gene sequences disclosed in granted U.S. patents to known mRNA sequences in a national database.[37]

In a critique, Christopher Holman's paper in *Nature Biotechnology* indicates that there is a misinterpretation of the dataset used in the Jensen and Murray article. The main issue is the interpretation of a patent claims which defines the scope of the invention.

> … the myth that 20 per cent of human genes are patented has taken root because so many have failed to appreciate the critical distinction between a DNA or amino acid sequence being 'mentioned' in a patent claim and a gene being 'claimed'.[38]

Furthermore, Holman's analysis of the Jensen and Murray dataset found that,

> one-quarter of the sampled patents do not claim a DNA molecule corresponding in sequence to a naturally occurring gene.[39]

All proteins are coded by genetic sequences, however, some patents can claim a protein without providing a genetic sequence. Holman also argues that another misinterpretation of the dataset relates to patents claiming microarrays. These type of patents claim specific probes derived from portions of cDNA sequences — in some cases over a thousand probes — the granted patent would only prevent others from using the exact same set of probes in the microarray.

Jensen and Murray do, however, highlight that there are differences in the number of isolated human gene patent in prior reports due to wrong analysis of claims and the

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36 Jensen, K & Murray, F, 'Intellectual Property Landscape of the Human Genome', 2005, Policy Forum, *Science*, 310:5746, pp. 239–240.

37 The methodology involved linking nucleotide or gene sequences found in granted patents to protein-encoding messenger RNA (mRNA) contained in the National Center for Biotechnology Information (NCBI) databases RefSeq and Gene. Jensen, K & Murray, F, 'Intellectual Property Landscape of the Human Genome', 2005, Policy Forum, *Science*, 310:5746, pp. 239–240.

38 Holman, M, C, 'Debunking the myth that whole-genome sequencing infringes thousands of gene patents', 2010, *Nature Biotechnology*, Vol 30, No. 3, pp. 240–244.

39 Holman, M, C, 'Debunking the myth that whole-genome sequencing infringes thousands of gene patents', 2010, *Nature Biotechnology*, Vol 30, No. 3, pp. 240–244.

controversy regarding what constitutes a 'gene patent'.[40] This makes it particularly important to properly define an isolated human gene patent, and to distinguish between various types. The reason being, different claim sets of gene patents determine the restrictions placed on other researchers and firms. For example, patents that claim a portion of an isolated gene sequence or method of using an isolated gene sequence does not preclude others from performing research on the full-length isolated gene sequence. In this report, we overcame that issue by asking patent examiners in the relevant field to read the claims in each sampled patent in order to allow us to estimate the number of isolated human gene patents with relevant claims, as discussed in chapter 3.

The second misconception over gene patents is that they grant ownership over human material. When a patent claims a genetic sequence found in humans, the patent holder does not own any physical material of any person. A gene patent does not impinge on the freedom of individuals to use their DNA.[41] Rather, a granted patent provides the inventor with the right to use that intellectual property for a period of time and to exclude others from this use, unless they have a license or are otherwise authorised to do so.

It is this latter point that generates the economic issues (both benefits and costs) that are the subject of this report.

40 Jensen, K & Murray, F, 'Intellectual Property Landscape of the Human Genome', 2005, Policy Forum, *Science*, 310:5746, pp. 239–240.

41 IP Australia/DIISR, Senate Committee Community Affairs: Inquiry into Gene Patents, Section 5.7.

2 Economic activity associated with isolated human gene patents in Australia

There are a wide range of entities involved in research and commercialisation activities in the human genetics area. For some, isolated human gene sequence patents are associated with only a small (but often growing) proportion of total activity, while for others, all business activity is underpinned by a patent for a human genetic technology.

It is estimated that $795 million is being invested in R&D associated with human genes in Australia, around 21 per cent of which is estimated to be private sector investment (for profit and not-for-profit).

The Australian pharmaceutical and biotechnology sector is estimated to invest in the order $167 million in R&D associated with human genetic research. Spillover benefits of 25 cents to 80.5 cents in the dollar are also likely to accrue to Australia, depending on the type of R&D performed.

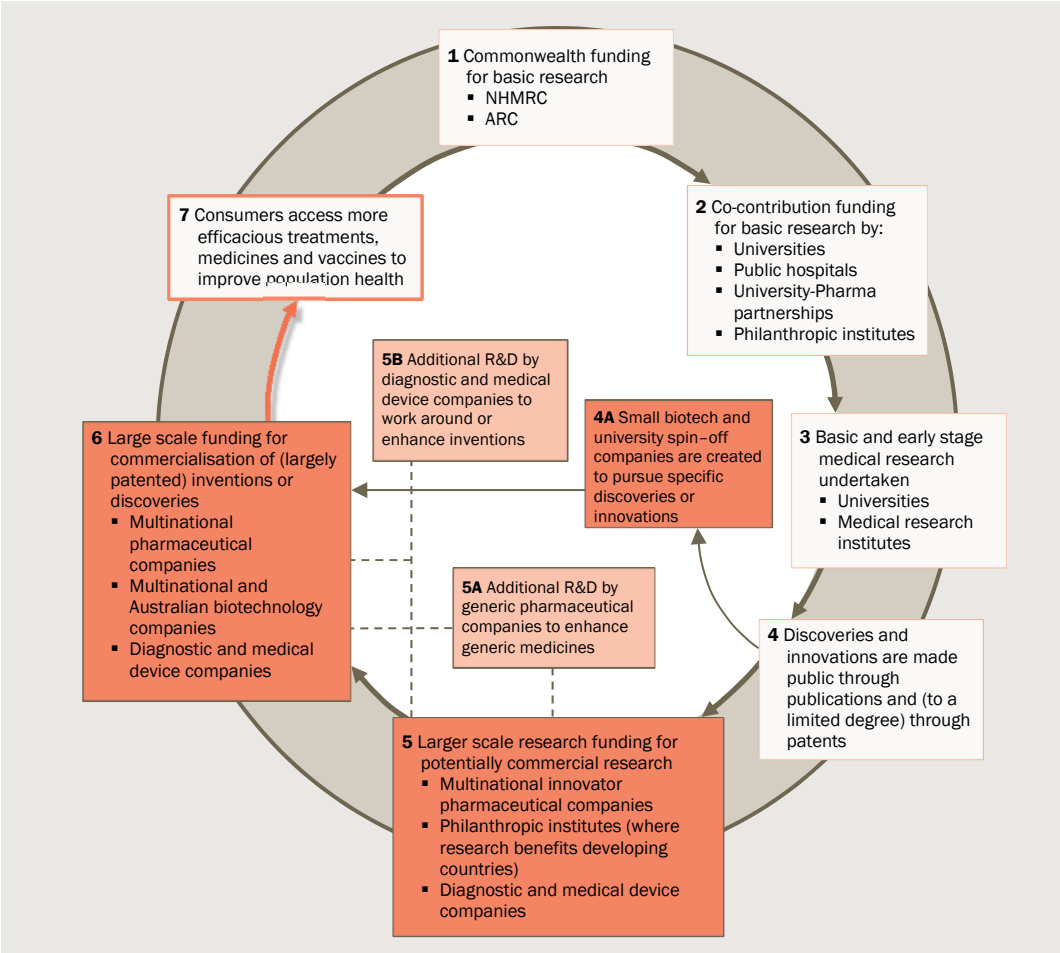
In 2011–12, medicinal and pharmaceutical product exports totalled over $4 billion. There are over 300 biotechnology companies in Australia that focus specifically on human therapeutics and diagnostics and around 41 000 people are employed in pharmaceutical manufacturing, wholesaling, R&D and biotechnology. The sector also attracts some foreign direct investment in Australian R&D, with approximately $25 million estimated to flow annually into human genetic related research (mainly Phase 3 clinical trials) in Australia.

Entities involved in research and commercialisation activities involving isolated human gene patents

There are a wide range of public and private entities involved in some way in the research and commercialisation of isolated human gene related inventions and discoveries that ultimately improved diagnostics, therapeutics and treatments.

This is due to the process of providing access to isolated human gene related health interventions typically involves public investment in basic medical research, public and private sector partnerships to progress towards the commercialisation of research, and the large scale investment by (typically) large multinational pharmaceutical and well financed biotechnology firms to translate research outcomes into new products. The public-private partnership involved in human genetic research is illustrated in chart 2.1. Some elements are contingent on the patent regime, others are ignited by patented research, and some are less, or only marginally affected by the IPR system.

2.1 Inputs across the public and private sectors that provide consumer access to human gene based therapies



Source: The CIE.

Total expenditure on human gene related research

The Australian Bureau of Statistics (ABS) reports on gross expenditure in medical and health sciences R&D, a proportion of which would be related to human gene related research. This data is reported in several ways.

For the purpose of this study, the most relevant presentation of the data is by field of research (for the 'medical and health sciences' category), or by socio economic area (the clinical health data set under the 'health' objective, and the human pharmaceutical products data set under the 'manufacturing' objective).

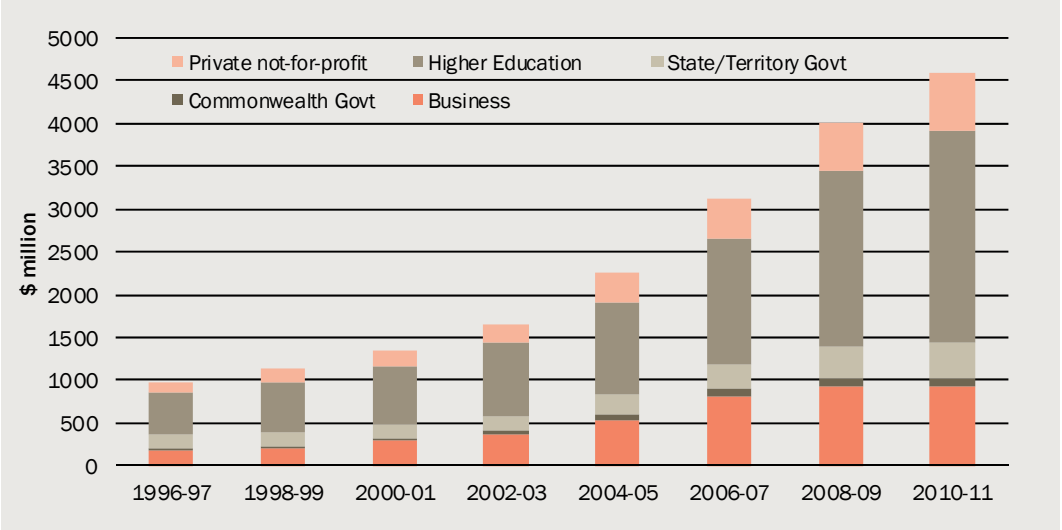
For both data presentations, the latest report from the ABS states that over $4.0 billion was spent on medical and health sciences R&D in 2008–09, including spending by business, government, higher education, and private non-profit entities.

In order to update this estimate, ABS data for Business Gross Expenditure on R&D (GERD) for 2010–11 has been used, which also reported GERD for the government, higher education and private not-profit sectors at the aggregate level (not by field of research or socio-economic objective or their components). Using the reported GERD by

field of research for Business R&D, and derived estimates for other sectors, a total of $4.6 billion is estimated to have been spent on medical and health sciences R&D in 2010–11 (chart 2.2). The equivalent estimate for relevant data by socio-economic area is $4.8 billion in 2010–11.[42]

This represents strong growth in R&D expenditure on medical and health sciences, which has grown at a compound annual growth rate of 12 per cent per annum since 1996-97.

2.2 Gross expenditure on R&D for the medical and health sciences field of research



Note: Due to the ABS's postponement of 2010–11 Government and Private Non-Profit collection, it is not possible to derive a perfectly comparable estimate of GERD in the same manner in 2010–11 and had been reported previously. The ABS also acknowledges that its estimates of GERD in 2010–11 have been 'carefully modelled' to provide a 'best estimate' of GERD in 2010–11 for these sectors.

Data source: Data from 1996–-97 to 2008–09 is drawn from ABS 2010, Research and Experimental Development, All Sector Summary, Australia, 2008-09, October. Data for 2010–11 is drawn (or derived by the CIE) from ABS 2012. Research and Experimental Development, Business, Cat. No. 8104.0, September.

While expenditure from all sources has grown, it is funding through higher education that has driven the vast majority of growth. This is partly due to the growth in National Health and Medical Research Council (NHMRC) funding over this period (as explained further below).

R&D attributable to human genetics

Determining the proportion of total R&D expenditure in Australia *that relates to human genetic research* is difficult given the available data.

42 The 2010–11 GERD data referred to in this report uses the published estimate for Business GERD by field of research and socio-economic area, and derived estimates for other sectors based on growth at the sectoral level between 2008–09 and 2010–11, applied to reported disaggregated GERD for 2008–09. The 2010–11 estimates imply that medical and health sciences R&D grew at a faster rate than total GERD between 2008–09 and 2010–11.

Clearly not all medical and health related R&D will be genetic research, and not all genetic research will relate to human genes. In some cases, it is difficult to distinguish human genetic research from other types of genetic research.[43]

As a guide, the NHMRC identifies research that it funds related to human genetics and genomics issues, which in 2012 accounted for 21.5 per cent of total NHMRC funding. The fields of research within this classification are too broad for the purpose of identifying human gene related research only.[44] However, based on analysis by IP Australia, approximately 98 per cent of this research is reasonably considered to be related specifically to human gene-related research, and excludes areas such as genetic counselling. The total expenditure on relevant R&D is equivalent to 21 per cent of total NHMRC funding.

This rate is considered to be a reasonable proxy for the amount of public sector and university R&D funding that is likely to relate to human genes, given these entities are the recipients of NHMRC funding. While the proportion of human-gene related R&D by business and non-profit entities may be similar, the distribution of NHMRC funding may be less useful as a proxy for private sector investment.

The proportion of private sector medical and health sciences R&D that may be human gene related is likely to be best represented by the proportion of medicines developed from biologics for pharmaceutical companies operating in Australia,[45] which was estimated by Medicines Australia to be 18 per cent in 2006.[46]

Applying these shares to public and private sector medical and health sciences R&D suggests there is approximately $795 million currently being spent annually on human genetics R&D in Australia (chart 2.3).

A summary of the entities that help fund and deliver this research is set out in table 2.4 and described further below.

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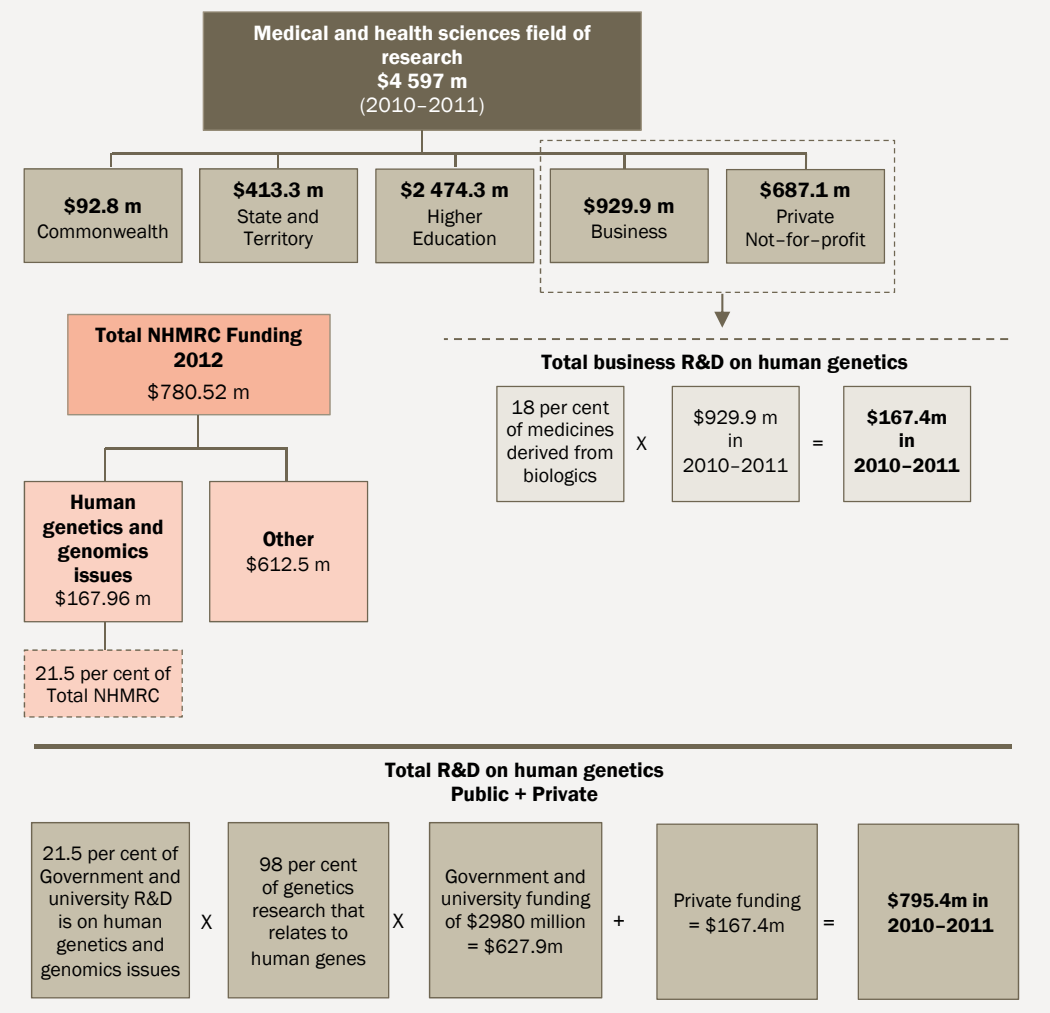
43 This arises because science is normally established in other organisms before work on human patients is performed, such as for model organisms like zebrafish, mice, the fruit fly and in some cases primates. Other research that may appear to be related to human genetic research may not be. For instance in the area of proteomics, research may relate to the structure and function of proteins (the coded product of a gene), or to the proteins in pathogens (bacteria and viruses).

44 The fields of research included in this category include gene expression, gene therapy, genetic development (incl. sex determination), genetic epidemiology, genetic immunology, genetic technologies (such as transformation, site-directed mutagenesis), genetics not elsewhere classified, genome structure, immunogenetics, medical genetics, neurogenetics, population and ecological genetics, and quantitative genetics.

45 Based on its own survey, Medicines Australia estimated that 18 per cent of medicines produced by pharmaceutical companies operating in Australia were developed from biologics in 2006 (Medicines Australia 2010, The Australian pharmaceuticals industry: the winds of change, Medicines Australia, Canberra, p. 14). While the survey forecast this proportion would rise to 27 per cent in 2012, the actual finding for 2006 has been used as a conservative measure.

46 Medicines Australia 2010, The Australian Pharmaceuticals industry: the winds of change, Medicines Australia, Canberra, p. 14.

2.3 Estimated gross expenditure on human gene-related R&D



Source: The CIE

2.4 Summary of estimated human gene related R&D 2010-11

Entity	Human gene R&D	Comment-
Government funded	$627.9 million	
NHMRC	$165 million	Assumes human genetic research accounts for 98 per cent of funding on human genetics and genomics.
Australian Research Council	Not estimated	Biological sciences and biotechnology funding was $57.4 million in 2012.
Cooperative Research Centres	Not estimated	$276 million is spent on medical related CRCs over their funding cycle
CSIRO	Not estimated	More than $150 million is invested in health-related research
Cancer Australia	Not estimated	Examples of funded genetic research are readily identifiable
Privately funded	$167.4 million	Assumes R&D in human genes is represented by the proportion of medicines developed from biologics for companies operating in Australia.
University-industry partnerships	Not estimated	Total Australian industry funding to universities is $351 million, some per cent of which is human gene related
Industry contributions to CRCs	Not estimated	36 per cent of the essential participants of active health related CRCs are industry aligned

Source: The CIE.

Funding for basic research and seed funding for commercialisation

There is a considerable amount of basic research effort in Australia involving human gene based research. While not often patent-related, those involved in basic research are strongly motivated by the desire to have their research realised in (downstream) clinical practice.[47] As research becomes more translational and relevant to medicines, therapeutics and vaccines, patents, be they isolated human gene patents and/or other patents covering modified genes or method (use only) claims, typically become central to the business model of bringing new products to market. Hence, basic research is an important precursor to the commercialisation of research, and without it, there would be substantially less human gene related medicines, treatments and vaccines available to consumers (and less economic activity associated with commercialisation activity downstream).

By and large, human genetic research begins with the public funding of basic research through a variety of channels, such as Commonwealth funding of the NHMRC, the Australian Research Council (ARC), and Cooperative Research Centres (CRCs).

The data shown on expenditure provided by public and private sector entities will be a subset of the total estimate of human genetics research set out in table 2.4.

NHMRC funding

The total envelope for NHMRC funded medical research is $857.6 million in 2013.[48] $168 million of research into human genetics and genomics issues was funded by the NHMRC in 2012. This NHMRC contribution has grown by two and a half times over the past decade alone.

Chart 2.5 shows NHMRC funding for human genetics and genomics issues by type of research over the past 12 years — this provides a useful gauge of the key growth areas of human genetics research in Australia. Most NHMRC funding flows to universities. Universities have a strong research base and play a key role in genetic based research in Australia. Universities received 72 per cent of NHMRC funding from 2003–12 ($584 million in 2012 alone). It should be noted that the research categories shown in chart 2.5 are not mutually exclusive as some grants straddle multiple research fields, and would therefore be double-counted in the data shown.

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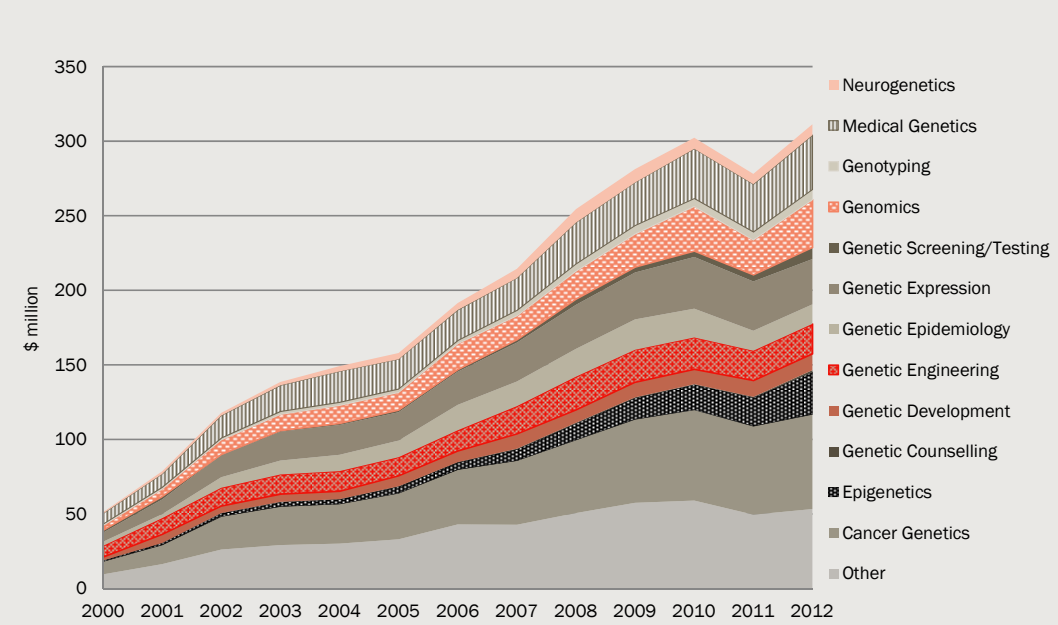
47 In the majority of cases, publicly funded human genetic research is of a public good nature, with greatest merit in the free distribution of research outcomes. Most of this type of research is not patented, and would not satisfy the criteria for patentability.

48 http://www.nhmrc.gov.au/grants/research-funding-statistics-and-data/nhmrc-research-funding-datasets-1990–2010/summary-annual

2.5 NHMRC funding for human genetics and genomics issues by type of research



Note: Many grants address more than one disease/condition type and may be reported in more than one type. Therefore the total of each type is a discrete total and aggregating all funding for the specific types will not equal total funding.

Data source: NHMRC 2012, http://www.nhmrc.gov.au/grants/research-funding-statistics-and-data/funding-datasets/human-genetics-and-genomics-research.

Medical research institutes (MRIs) generally receive the balance of NHMRC funding. There are 37 medical research institutes across Australia, which received 23 per cent of NHMRC funding ($181.9 million) in 2012.[49] NHMRC funding administered by each MRIs over the past nine years is shown in table 2.6, which identifies MRIs that have received more than 1 per cent of NHMRC funding over the nine year period. These MRIs received $1474 million over that time period, and accounted for 26 per cent of all NHMRC funding.

2.6 Distribution of NHMRC expenditure to MRIs, 2003–2012

MRI that funds were granted to	NHMRC funding 2003–12 $ million	Share of NHMRC funding 2003–12 Per cent
Walter and Eliza Hall Institute	342.92	6.0
Queensland Institute of Medical Research	211.33	3.7
Baker IDI Heart and Diabetes Institute	161.22	2.8
Murdoch Children's Research Institute	149.79	2.6
Garvan Institute of Medical Research	147.72	2.6
Prince Henry's Institute of Medical Research	62.82	1.1
Menzies School of Health Research	62.13	1.1

(Continued next page)

49 This figure excludes grants for research that may be administered by an associated university.

2.6 Distribution of NHMRC expenditure to MRIs, 2003–2012 (Continued)

MRI that funds were granted to	NHMRC funding 2003–12	Share of NHMRC funding 2003–12
	$ million	Per cent
St. Vincent's Institute of Medical Research	60.40	1.1
Macfarlane Burnet Institute for Medical Research and Public Health	59.85	1.1
Victor Chang Cardiac Research Institute	48.04	0.8
Ludwig Institute for Cancer Research	43.57	0.8
Children's Medical Research Institute	22.81	0.4
Mater Medical Research Institute, Brisbane	18.15	0.3
Menzies Research Institute	17.22	0.3
Centre for Eye Research Australia Ltd	14.60	0.3
Heart Research Institute	13.89	0.2
National Stroke Research Institute	8.92	0.2
Howard Florey Institute	7.69	0.1
Mental Health Research Institute of Victoria	6.85	0.1
Brain Research Institute	4.63	0.1
Schizophrenia Research Institute	3.47	0.1
Austin Research Institute	3.31	0.1
Institute for Breathing and Sleep	2.93	0.1
Total for all MRIs listed above	1 474.28	26.0

Note: MRIs that received less that 0.1 per cent of NHMRC funding have been excluded.

Data source: NHMRC research funding datasets 1990–2012 and the CIE.

Australian Research Council

The ARC funds research in the National Research Priorities, which includes promoting and maintaining good health by 'counteracting the impact of genetic, social and environmental factors'. Total funding for biological sciences and biotechnology was $57.4 million in 2012 (24 per cent of total funding). Further, $41.9 million (over 153 projects) was allocated to the promoting and maintaining good health National Research Priority.[50] A proportion of this funding would be related to human gene based research.

Cooperative Research Centres

Several CRCs are aligned with the medical science and technology sector, some of which involve public-private partnership investment to undertake human gene related research. This includes the CRC for Biomedical Imaging Development, the CRC for Cancer Therapeutics, the CRC for Biomarker Translation, HEARing CRC, Oral Health CRC and the CRC for Mental Health, the Vision CRC, CRC for Aboriginal and Torres Strait

50 Australian Research Council, *Summary of Discovery Projects 2012 Funding.*

Islander Health, CRC for Asthma and Airways and the Young and Well CRC. CRCs received $276 million in CRC program funding spread over the lifetime of the CRC.

A subset of this research is human gene related research. For instance, the CRC for Biomarker Translation develops antibodies directed against therapeutic and diagnostic targets (biomarkers) present on cells that play a key role in major diseases. Gene microarray analysis enables the interrogation of these cells for biomarker discovery. The CRC for Mental Health seeks to identify and validate biomarkers for the early detection and treatment of neurodegenerative disorders and psychoses, which include specific cells, molecules, genes, gene products, hormones, or subtle brain image changes.[51]

Commonwealth Scientific and Industrial Research Organisation

The CSIRO invests more than $150 million annually in health-related research across nutrition, disease prevention, biomedical devices and implants, medical imaging and information processing. Human genetic research forms an important component of the CSIRO's workplan. For instance, the CSIRO has expertise and is active in molecular science, including producing recombinant proteins for structural and therapeutic studies, developing novel biomaterials as implants and translating gene expression signatures into candidate protein biomarkers.[52]

Cancer Australia

Cancer Australia administers several grant programs providing support for cancer research, cancer clinical trials and cancer support networks. In 2011, it funded 30 grants totalling $9.35 million, which included research on 'high risk genes for lobular breast cancer' and 'gene expression profiles of aggressive metastatic triple negative breast cancer'.[53]

Industry partnerships for basic research delivery

Government investment in human gene research is a significant attractor of private sector interest in human gene related research and translation in Australia. Joint public-private research would typically be in the preliminary stages of being translational, moving from basic research into more commercial phases of research.

A mapping study on Australian industry-university linkages highlighted that in the medical research area, partnerships with universities and MRIs are a key element of the innovation paradigm and that the proximity to basic research is critical to successful research outcomes.[54]

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51 CRC Directory: Cooperative Research Centres Program 2011–12.

52 CSIRO 2009, Health and wellbeing brochure, November.

53 Cancer Australia, Priority-driven Collaborative Cancer Research Scheme 2012.

54 ARC, Mapping the nature and extent of Business-University interaction in Australia, Commonwealth of Australia, Canberra, p. 34. This study focuses specifically on links with universities although links with MRIs are equally applicable.

University-industry partnerships

Of the $3252 million in external research income received by universities in 2011, $701 million was from non-Government sources (excluding domestic and international student fee income), of which $351 million was from contracts with, or grants from, Australian based companies (table 2.7).

There is no available data on the subset of Australian company funding of university research that relates to medical science, or within that, human genetics.

A particularly notable example of patented university-based research in the human genetics area is the Papilloma Virus Vaccines, which was recently brought to market by GSK (Cervarix) and Merck (Gardasil) to prevent cervical cancer (see box 2.8).

2.7 Industry and other funding for Australian university research 2011

Australian industry contracts	Australian industry grants	Australian donations bequests and foundations	International A: Competitive, peer-reviewed research income	International B: Other income	Total non–government and non–student income
$'000	$'000	$'000	$'000	$'000	$'000
219 072	132 076	179 140	72 479	98 260	701 029

Source: Department of Industry, Innovation, Science, Research and Tertiary Education 2011, *2011 Income and Publications data by subcategory*.

Industry contributions to medical CRCs

The CRC program links researchers with industry to focus R&D efforts on utilisation and commercialisation. As such, private industry and industry associations offer critical support to health related CRCs. Active health CRCs had 70 essential participants as at July 2012, of which 36 per cent were industry aligned. Since the inception of the CRC program in 1991, the Australian Government has committed more than $3.4 billion in funding and other participants have committed a further $10.9 billion in cash and in-kind contributions to all CRC, part of which relates to health-related CRCs.

Commercial research: moving towards translational outcomes

There are a range of companies operating in Australia that undertake research relating to human genes, in addition to their partnership activities with publicly funded entities.

2.8 Patented university based research underpinning the vaccine for cervical cancer

For 25 years, Professor Ian Frazer, of the University of Queensland, pursued an interest in development of vaccines to prevent human papillomavirus (HPV) infection. In 1985, with colleagues in Melbourne Professor Frazer demonstrated that papillomavirus infection also contributed to anal precancer, particularly in men with immunosuppression as a result of HIV/AIDS. In 1990, Professor Frazer and his then postdoctoral scientist, Dr Jian Zhou, developed the technology for producing human papillomavirus virus like particles.

This technology, licensed through the University of Queensland, is now the basis of vaccines recently brought to market by GSK (Cervarix) and Merck (Gardasil) to prevent cervical cancer. The HPV vaccine is only the second vaccine to be produced using recombinant DNA technology, which was necessary because papillomaviruses could not be grown in cell culture.

The development of HPV virus like particles was an early product of the application of comparative genomics. Sequence alignment for the genes for the major capsid proteins of a range of papillomaviruses showed that expression of the major capsid protein of the HPV16 virus from the second initiation codon in eukaryotic cells was likely to induce particle formation where conventional expression strategies had failed.

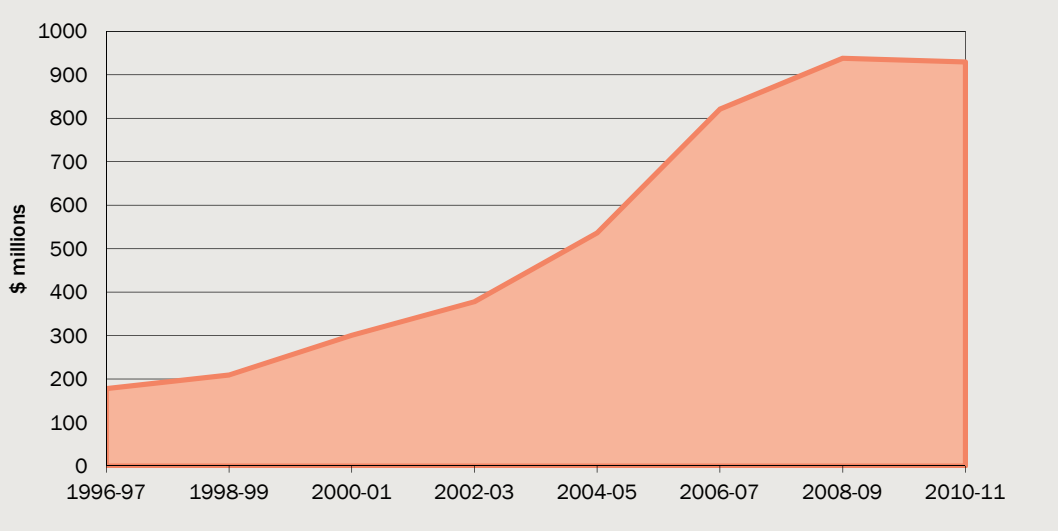
Professor Frazer has also developed two different therapeutic vaccines for chronic HPV infection, one currently in Phase 2b clinical trials through CSL Ltd and one in Phase 2b clinical trials in China and Brisbane with funding from the Cancer Research Institute of New York and The Wellcome Foundation. Professor Frazer has also developed a technology for improving the immune response to polynucleotide vaccines based on differential preferences for codon usage between cells of different lineages, which has been licensed to Coridon Pty Ltd and is currently being used to develop polynucleotide vaccines for Herpesviruses.

Source: http://www.go8.edu.au/go8-members/go8-committees/go8-deans-of-medicine/go8-medical-research-case-studies.

This includes more than 40 originator pharmaceuticals companies (most of which are subsidiaries of global corporations), around 10 generic medicine companies, over 500 core biotechnology companies, around 40 diagnostic public and private pathology services, and a variety of small university-based spin off companies.

Overall, Australian business expenditure on research and experimental development in the medical and health sciences sector has tripled over the previous decade (chart 2.9). The medical and health sciences sector spent $929.9 million on research and development in 2010–11 and accounted for 5 per cent of total (economywide) industry business expenditure.

2.9 Business GERD on the medical and health sciences field of research, before 2011

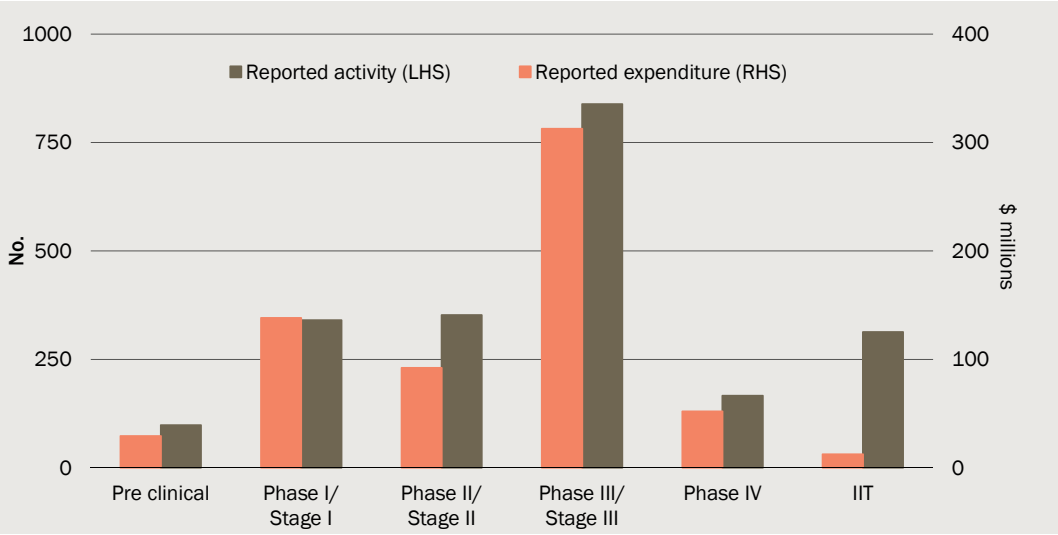


Note: Includes all businesses including the private non-profit entities mainly serving them.

Data source: ABS 2012, Research and Experimental Development, Businesses Cat. No. 81040D0007_201011 and the CIE.

The *2011 Survey of Privately Funded Clinical Research in Australia* is a web-based survey that aims to gauge the level of privately funded clinical research activity in Australia. Companies responding to the survey reported a total expenditure in 2010 of $636.5 million.[55] Expenditure on Phase III/ Stage III studies accounted for nearly half of the total. Further, respondent companies reported conducting 2107 studies in 2010 — Phase III/Stage III studies accounted for the largest share (40 per cent) of the total activity (chart 2.10).

2.10 Reported expenditure and activity in privately funded clinical research, 2010



Note: The survey was sent to the relevant members of AusBiotech, the Medical Technology Association of Australia, IVD Australia, Medicines Australia and to contract research organisations which are not members of any of the four associations.

Data source: Pharmaceuticals Industry Council 2012, 2011 Survey of Privately Funded Clinical Research Activity, February.

55 53 companies responded to the survey, including 28 'pharmaceutical companies', 14 'contract research organisations', seven 'medical device or medical technology companies', and four 'biotechnology' companies. The response rate was 50 per cent; however, the survey captures the majority of investment in clinical research in Australia.

The *2011 Survey of Privately Funded Clinical Research in Australia* also sheds light on where privately funded clinical research is conducted. While the majority of reported research was conducted at public hospitals (60 per cent), private research institutes contributed 15 per cent and private hospitals 12 per cent. Among 'other' locations, companies identified 'specialist clinics' and 'independent Phase I units'.[56]

With the exception of public diagnostic laboratories, these entities are commercially driven.

For all entities, research is more directly translational, as discoveries and inventions are put into clinical practice. The purpose of research is often to attract and/or justify significant private investment from overseas parent companies or venture capital. The type of research undertaken typically has a risk/reward profile that does not align with the principles of government funding for research.

Increasingly these entities are entering into commercial partnership arrangements with each other. The rise of biotechnology, which tends to be smaller in scale and more complex in resources required than traditional manufacturing operations, has seen innovative pharmaceutical companies go outside their corporate laboratories in search of new drug candidates. This has resulted in a rise in extramural R&D and the establishment of strategic alliances with small biotechnology companies opening new opportunities for capital raising by Australian biotech firms.[57]

The Australian biotechnology sector is capital-intensive and relies on accessing global capital markets. The Investment Company Institute reports that Australia has the world's third largest pool of investment fund assets.[58] Industry observers note that biotechnology companies tend to operate at a loss for 10 years with 50–60 per cent of companies typically in the capital-raising mode of business operations.[59]

It is expected that many of these pharmaceutical and biotechnology companies are currently, or potentially, involved in an isolated human gene patent based activity in some way.

Research and development by pharmaceutical and biotechnology companies operating in Australia

Pharmaceuticals are a knowledge-based, technology intensive industry that induces significant investment in research and development.

The Australian pharmaceutical industry is dominated by foreign-owned multinational enterprises. Generally, innovative pharmaceutical companies have tended to locate their corporate R&D laboratories in North America and Western Europe. Hence, issues of investment from the Australian perspective focus heavily on the attraction and retention of foreign direct investment in the pharmaceutical industry.

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56 Pharmaceuticals Industry Council 2012, 2011 Survey of Privately Funded Clinical Research Activity, February

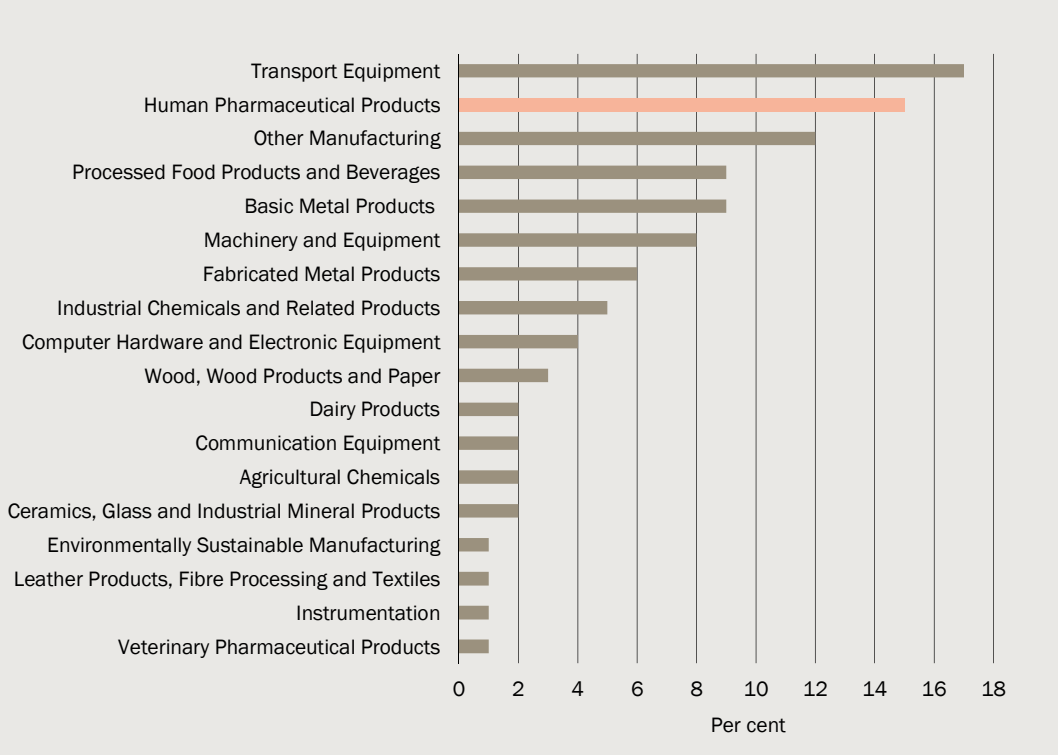
57 Allens Consulting Group 2006, *Drivers of Pharmaceutical Industry Investment*, prepared for Medicines Australia and Research Australia, September.

58 ASX 2012, *Health Care and Biotechnology Sector Profile*, November.

59 This was noted by stakeholders consulted from the Australian biotechnology sector.

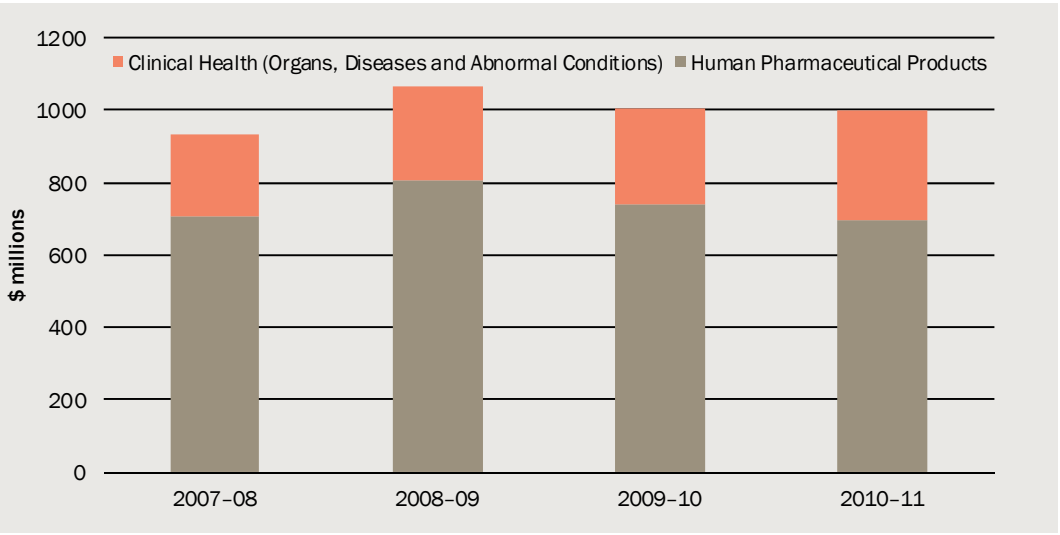
In Australia, the medicines industry is the second highest manufacturing industry investor in R&D, with $696.1 million in business expenditure on human pharmaceutical products (15 per cent of total manufacturing R&D) in 2010–11 (see chart 2.11). Including business expenditure on clinical health suggests that the medicines industry is responsible for almost $1 billion spent on research and development in the 2011 financial year. The majority of the R&D expenditure is related to human pharmaceutical products ($696 million of total expenditure in 2010–11), with the remainder devoted to clinical research into organs, diseases and abnormal conditions (chart 2.12).

2.11 Business expenditure on R&D — Manufacturing, 2010–11



Data source: ABS Research and Experimental Development, Businesses, 2010-11, Cat. No. 81040D0008_201011 and the CIE.

2.12 Pharmaceuticals and biotechnology business expenditure on R&D



Data source: ABS Research and Experimental Development, Businesses, Australia, 2010-11, Cat. No. 81040D0008_201011.

The Australian pharmaceuticals industry economic survey undertaken by Medicines Australia suggests that 79 per cent of respondents were engaged in R&D activities in Australia during 2007 and 2008. The survey concluded important insights about the R&D profile of private companies.[60]

- Nearly two-thirds of R&D conducted by respondents in 2008 related to either Phase II clinical research (15 per cent) or Phase III clinical research (48 per cent).
- The majority of the R&D conducted in Australia was conducted by Australian business units on their own behalf (37 per cent) and on behalf of their global parent/affiliates (49 per cent). The rest (15 per cent) was performed by their global parent/affiliate directly, for which the Australian business units were not responsible.
  - Of the R&D conducted by respondents' Australian business units on their own behalf, the majority (up to 85 per cent) was either performed in-house or contracted to, or in collaboration with, hospitals. A minority was, contracted to, or performed in, collaboration with a private research company.
  - Of the R&D conducted by Australian business units on behalf of their global parent or affiliate, the majority was either in-house (65–67 per cent) or contracted to, or in collaboration with, hospitals (18–20 per cent). A minority was either, contracted to, or in collaboration with, academia (10–11 per cent).

There is no firm evidence on how much pharmaceutical R&D in Australia relates to biologics[61] or biotechnology[62], which are more likely to be human gene related.

Globally, biotechnology medicines are said to account for around 10–15 per cent of the current pharmaceutical market, with more than one-fifth of new medicines launched on the world market each year now being biotechnology-derived.[63]

Based on its own survey, Medicines Australia has estimated that the percentage of medicines produced by pharmaceutical companies operating in Australia are developed from biologics which has risen from 18 per cent in 2006 to 27 per cent in 2012.[64]

While some biologics may be non-human, for the most part biologics would have genetic and protein material with a human origin.[65] Using the proportion of biologics in medicines as a proxy for the proportion of private sector investment in human genetic

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60 Medicines Australia 2010, *The Australian pharmaceuticals industry: the winds of change*, Medicines Australia, Canberra.

61 Biologics includes bio-therapeutic medicines, biological medicines and biopharmaceuticals.

62 Biotechnology includes the methods and techniques that involve the use of living organisms (such as cells, bacteria, yeast and others) as tools to perform specific industrial or manufacturing processes.

63 European Biopharmaceuticals (n.d.) What are biopharmaceuticals? http://www.ebe-biopharma.org/index.php?option=com_content&task=view&id=26&Itemid=102

64 Medicines Australia 2010, The Australian pharmaceuticals industry: the winds of change, Medicines Australia, Canberra, p. 14.

65 This may over-estimate the proportion of R&D activity by pharmaceutical and biotechnology companies operating in Australia, but alternative proxies (such as the distribution of patenting activity) have been discounted as being inadequate. An over-estimate is expected because some biologics may be based on proteins with a non-human origin, or based on modified sequences or modified antibodies, which have been excluded from the analysis in this report.

research, it is estimated that approximately $167 million is being invested by the Australian pharmaceutical sector in areas associated with human genetic research.

Knowledge spillovers from pharmaceuticals R&D

A large body of literature has concluded that R&D generates a significant stock of new knowledge that can be used and appropriated by those that do not pay for the generation of this knowledge. Aside from the creation of new knowledge, pharmaceuticals research is beneficial in that physically conducting the research in Australia (as compared to an overseas location) further increases the spillover benefits accruing to Australia in the form of health benefits.

For instance, where pharmaceutical R&D relates to clinical trial activity in Australia, patient access to clinical trials has an important health impact in terms of speeding up access to the latest medical treatments. While not all patients in a trial receive the new drugs/therapies being tested, all patients are placed in the care of the leading/specialised clinicians involved in the trial and are hence in the 'best possible place'.

Australian hospitals also benefit when clinical trial activity is undertaken in Australia as a result of their payment for participation in trials through cost-recovery mechanisms. A survey by Medicines Australia indicates that Australia's Phase I clinical trial sector employs over 300 people and earns $50 million per annum in revenue, mostly from overseas companies.[66]

Spillover benefits from pharmaceutical R&D have been estimated at ranging from 25 cents to 80.5 cents depending on the type of R&D performed (table 2.13).

2.13 Estimation of spillovers associated with pharmaceuticals R&D

	Productivity Commission	CIE	Deloitte
	%	%	%
Basic/Pre-clinical R&D	57.5	61.0	57.5 – 80.5
Clinical R&D	25.0	61.0	25.0 – 35.0

Note: The CIE combined spillovers arising from both additional and novel R&D activity to arrive at this figure. Deloitte estimates have a broad range because it covered the two different payment rates offered under P3. Deloitte treated Phase I clinical trials as the same as basic and pre-clinical R&D in terms of the spillovers it generated.

Data source: Productivity Commission (2003), Evaluation of the Pharmaceutical Industry Investment Program; Centre for International Economics (2006), First year evaluation of the Pharmaceuticals Partnerships Program; and Deloitte Insight Economics, (2008) First year evaluation of the Pharmaceuticals Partnerships Program.

University spin off companies

Research organisations create spin-off companies as a means of holding and developing patented technology. According to the DEST Collaboration Review, university spin-off companies are often established out of necessity due to the lack of companies seeking to develop university generated intellectual property in Australia.[67] The National Survey of

66 Pharmaceuticals Industry Strategy Group, Final Report, December 2008, p. 35.

67 Department of Education Science and Training 2004, *Review of Closer Collaboration between Universities and Major Publicly Funded Research Agencies,* p. 30.

Research Commercialisation suggests that from 2000 to 2011, universities have created 332 new start-up companies.

There are various examples of university spin-off companies that have evolved to exploit an isolated human gene based invention or discovery. The largest proportion of these have been established to market and licence technology, rather than to develop and market a product[68] due to the higher investment costs required to bring a product to market.

For instance, Nanomics BioSystems Pty Ltd is a biotechnology start-up company focused on commercialising a platform technology spanning the fields of genomics, drug discovery, and human diagnostics. The technology was developed by founder Associate Professor Matt Trau from the University of Queensland. It provides a unique method for barcoding libraries of silicon beads with labels identifying individual chemicals attached to their surfaces. Potential applications include rapid DNA sequencing, comparative genomics, genetic screening, pharmacogenomics, and combinatorial drug discovery.[69]

Impacts on economic activity in Australia

The pharmaceutical, biotechnology and diagnostic sectors comprise an important sector of the Australian and global economy. In 2011–12, the pharmaceutical sector was one of Australia's largest contributors of manufactured exports, with medicinal and pharmaceutical product exports totalling over $4 billion.[70] Industry turnover has doubled over the past decade to $22.46 billion in 2010–2011. Domestically, the pharmaceuticals industry employs approximately 41 000 people, including areas in manufacturing, wholesaling, R&D and biotechnology.[71] The industry also attracts some foreign direct investment in Australian R&D.

Industry turnover

The pharmaceutical industry has expanded rapidly over the past decade with turnover (including manufacturing, sales and distribution) doubling from $10.4 billion in 1999-2000 to $22.46 billion in 2010–2011 (chart 2.14). The rate of growth has pared back substantially in recent years as the sector adjusts to significant changes in the global pharmaceutical market as long-standing blockbuster medicines reach the end of their patent protected exclusivity period.

Employment

In Australia the pharmaceutical sector employs an estimated 41 000 people including areas in manufacturing, sales and distribution in 2009–10. This has increased by over 20

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68 ARC 2001, Mapping the nature and extent of Business-University interaction in Australia, p. 49, Commonwealth of Australia, Canberra.

69 The University of Queensland Australia, Research Highlights, 2001.

70 ABS 2013, International Trade in Goods and Services, Australia, Cat. No. 5368.0, February.

71 The Department of Industry, Innovation, Science, Research and Tertiary Education, Australian Pharmaceuticals Industry Data Card 2011.

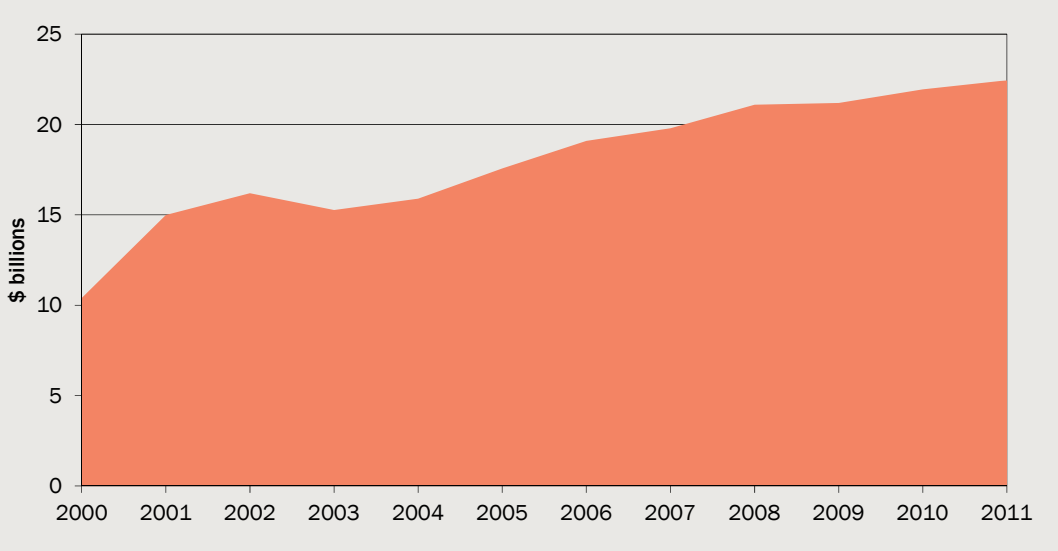
per cent from just over 34 000 full time equivalent employees in 2002–03.[72] While total pharmaceutical and biotechnology manufacturing employment has edged down since 2004 to 13 375 people in 2010, employment in the aggregate biotechnology sector has bucked the trend and risen strongly since the mid-2000s.

Chart 2.15 provides a detailed breakdown of industry employment, illustrating that the majority of growth up to 2007 was from the biotechnology sector. The proportion employed in areas relating to human genetics research is unknown, but is expected to be relatively small but growing strongly.

The 2011 Survey of Privately Funded Clinical Research Activity suggests those respondent companies' employ 1416 people in clinical research-related roles — with clinical research associates accounting for more than half of the total (table 2.16).

There are also currently over 1000 full time equivalent people employed in medical genetic laboratories, the majority of which would be involved in human genetic testing (see table 2.17).

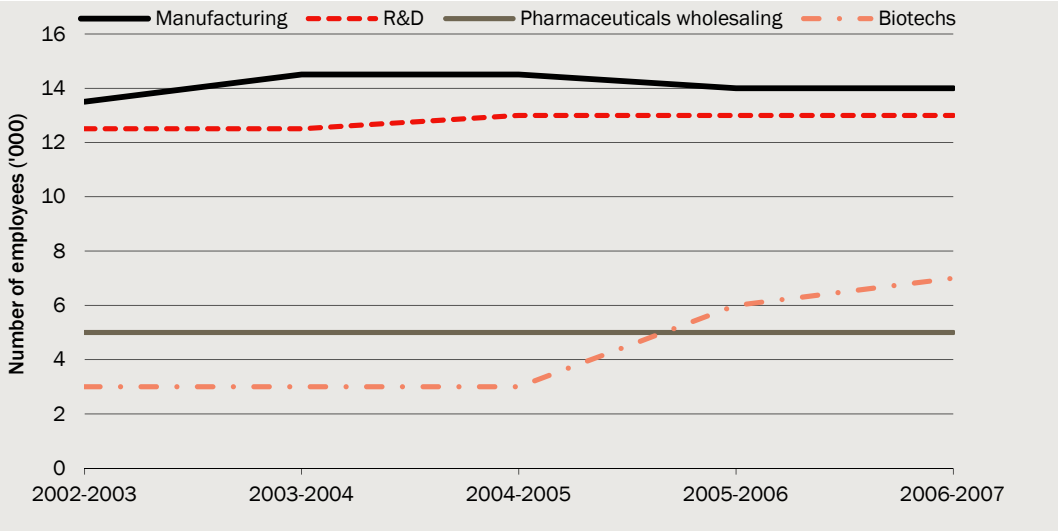
2.14 Australian pharmaceuticals industry turnover, 2000–2010



Data source: The Department of Industry, Innovation, Science, Research and Tertiary Education, Australian Pharmaceuticals Industry Data Card 2011.

72 The Department of Industry, Innovation, Science, Research and Tertiary Education, Australian Pharmaceuticals Industry Data Card 2011.

2.15 Breakdown of pharmaceuticals and biotechnology industry employment growth, 2003–2007



Data source: Pharmaceuticals Industry Strategy Group, Final Report, December 2008.

2.16 Employment reported by privately funded clinical research, 2010

Employee type	Number employed No.	Share of total Per cent
Clinical Research Associate	794	56
Clinical Research Manager	176	12
Clinical Research Director	58	4
Other	388	28
Total	1416	100

Data source: Pharmaceuticals Industry Council 2012, 2011 Survey of Privately Funded Clinical Research Activity, February.

2.17 FTE staff employed in medical genetic laboratories, 2011

	Total FTE	FRCPA [a] (genetics)	FRCPA (other)	FHGSA	Other Fellow	MHGSA	Other Med Scientist	Technician
NSW	238.6	3.8	5.2	18.2	3.1	24.8	160.9	22.7
Qld	230.2	4.2	10.6	8.5	6	28.4	143.2	29.3
SA	174.4	2	1	3	7	17	62.1	82.3
Tas	9.2	0	0	0	0	2	4	3.2
Vic	221.5	0.1	3.7	16.2	4	25.6	133.9	38
WA	136.8	3.4	13	5	6	16	70.4	23
Total	1010.7	13.5	33.5	50.9	26.1	113.8	574.5	198.5

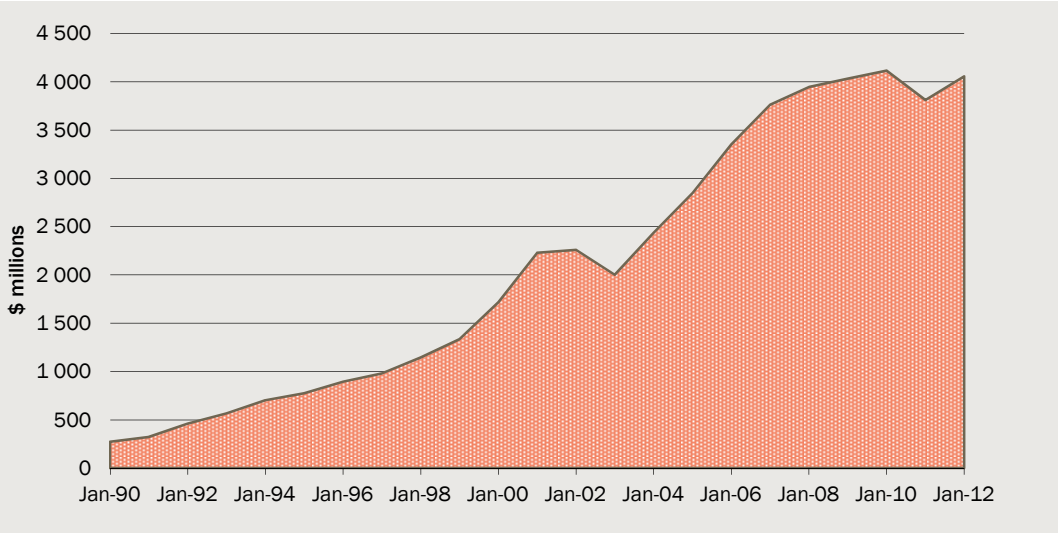
[a] FRCPA refers to Fellow of the Royal College of Pathologists of Australasia

Data source: Royal College of Pathologists of Australasia 2012, *Report of the RCPA Genetic Testing Survey 2011*, December, p.29.

Exports

Australian exports of pharmaceuticals have grown dramatically over the past 20 years and in 2012 exports totalled over $4 billion of pharmaceutical merchandise (chart 2.18).

2.18 Australian medicinal and pharmaceutical product exports, 1990–2012



Data source: ABS, International Trade in Goods and Services, Australia, Cat. No. 5368.0.

Foreign Direct Investment

An Australian pharmaceuticals industry survey suggests that foreign direct investment in Australian R&D (investment by the global parent of Australian affiliates' which the local business unit is not responsible) is relatively small but significant. In 2008, FDI was found to account for 15 per cent of pharmaceutical R&D in Australia. In value terms, across both 2007 and 2008, seven survey respondents indicated that their global parents/affiliates conducted R&D in Australia totalling over $100 million.[73] A proportion of this would be related to human genetic research.

The survey also highlighted the growing importance of the early stage clinical trial sector. Australia has a growing Phase I clinical trial sector that employs over 300 people and earns $50 million per annum in revenue, mostly from overseas companies.[74]

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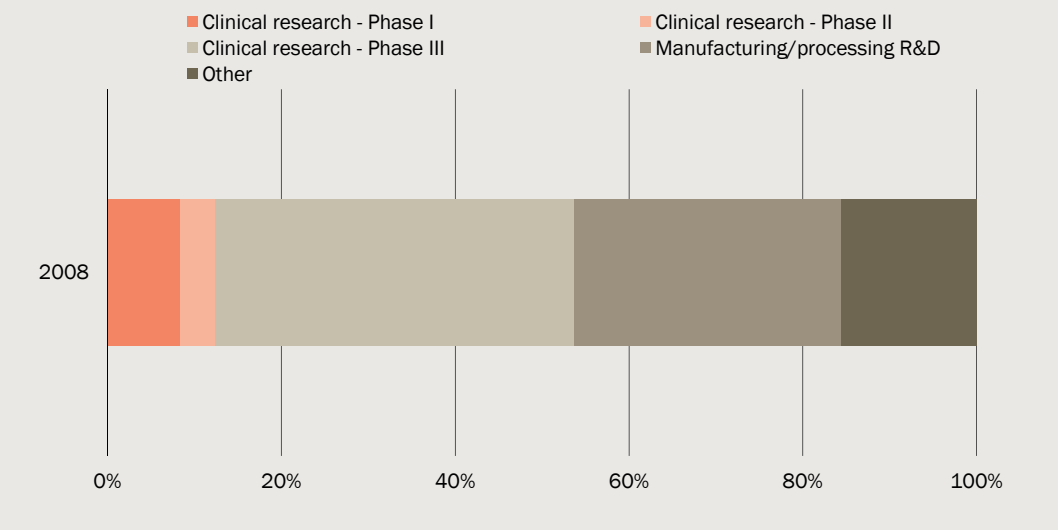
73 Medicines Australia 2010, The Australian pharmaceuticals industry: the winds of change, Medicines Australia, Canberra.

74 Pharmaceuticals Industry Strategy Group, Final Report, December 2008, p. 35.

2.19 Foreign direct investment in Australian R&D, by type of R&D

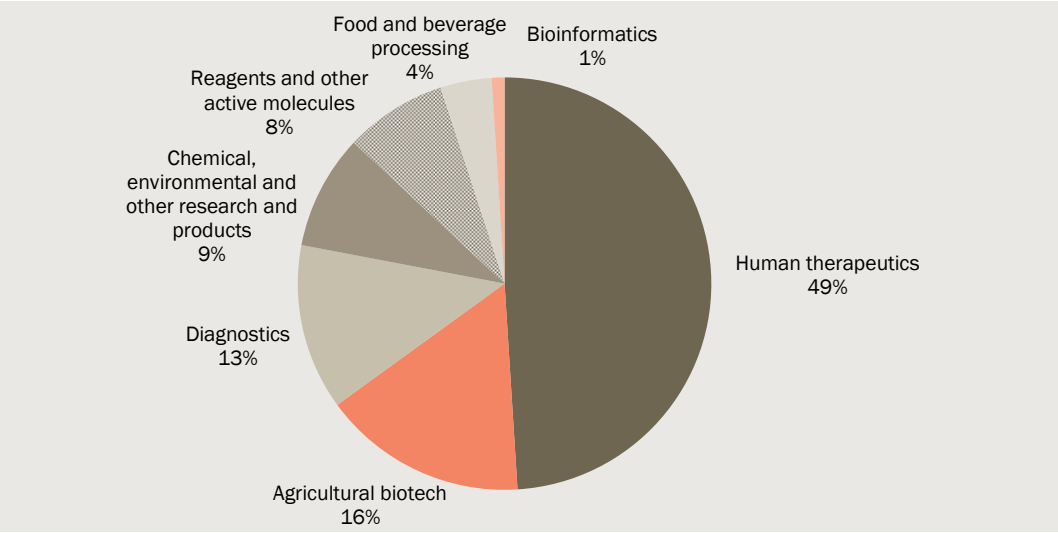


Data source: Medicines Australia 2010, The Australian pharmaceuticals industry: the winds of change, Medicines Australia, Canberra.

The Australian biotechnology sector

The Australian biotechnology sector incorporates over 500 businesses (including 100 listed companies) and more than 7000 staff (48 per cent of which are located in Victoria). Approximately 62 per cent (over 300 companies) of the current biotech businesses focus on human therapeutics and diagnostics (chart 2.20).

2.20 Distribution of Australian Biotech Businesses by sector



Data source: AusBiotech presentation by Dr Anna Lavelle.

The biotechnology industry is highly concentrated. Ten companies tracked by the Biotech Business Indicators (BBI) had a market capitalisation of more than $100 million. In 2011–12, these companies held $24.1 billion between them, or 97.6 per cent of the total market value of BBI-tracked companies. Including those with a market capitalisation of less than $100 million, total sector market capitalisation is $24.7 billion.

Australia's largest biotechnology company is CSL Ltd, which develops and manufactures blood plasma products, cell culture media, vaccines and anti-venoms. As at June 2012, CSL had a market capitalisation of $20.1 billion, or 81.4 per cent of the total market capitalisation of tracked companies. Ausbiotech suggests that the market capitalisation of listed biotechnology companies, including CSL, divided by GDP puts Australia first in the world in terms of the size of its biotech sector.

However, isolated human gene patents comprise only a minor component of CSL's business model. Therefore, the human gene specific biotechnology sector is likely to have a combined market capitalisation of around $4.6 billion, excluding CSL, (chart 2.21).

Diagnostics

Diagnostics is a broad medical specialty concerned with the nature and causes of diseases. Genetic pathology — an expertise in interpreting the results of laboratory genetic tests — is a small subset of the diagnostic field. Genetics represented just 1.2 per cent of total MBS expenditure on pathology services in 2009–10.[75]

The *Australian Genetic Testing Survey 2011* reports that diagnostics (or screening purposes) are the primary reason for performing medical genetic testing in Australia. The latest survey also suggests a significant increase in the scale and scope of genetic testing. Since 2006, there has been a 2.8 fold increase in the volume of molecular genetic assays performed annually,[76] and an increase in the number of targets tested (or types of tests available) from 437 to 546.[77] While the proportion of assays sent overseas has increased in recent years, this remains a relatively small percentage compared to the volume of assays performed within Australia.

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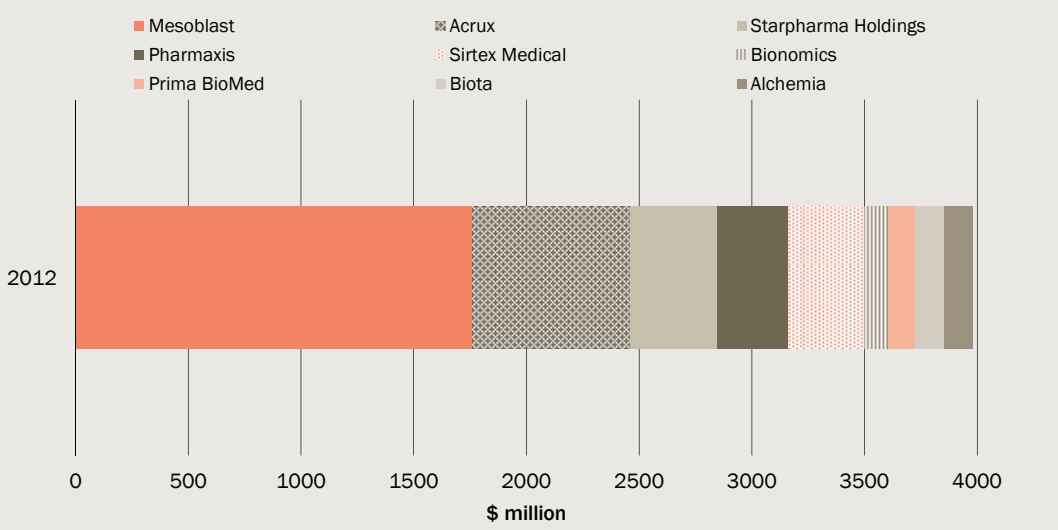
75 Department of Health and Ageing 2011, Review of the Funding Arrangements for Pathology Services, Final Discussion Paper, March, p. 15.

76 There was a total of 115 993 molecular genetic assays performed in 2006 and 327 193 molecular genetic assays performed in 2011

77 Royal College of Pathologists of Australasia 2012, *Report of the RCPA Genetic Testing Survey 2011*, December.

2.21 Australian biotech market capitalisation, 2012



Data source: The Department of Industry, Innovation, Science, Research and Tertiary Education, Biotech Business Indicators Q2 2012

Biologics: a key area of growth

Globally, the pharmaceutical sector is undergoing structural change, as the focus of research and investment increasingly transitions to biologics rather than single molecule medicines. Biologics (also known as bio-therapeutic medicines, biological medicines and biopharmaceuticals) cover a range of medicines derived from proteins and other substances produced by living organisms — for example mammalian cells, viruses and bacteria — and are likely to involve recombinant DNA technology.[78]

There is currently over 250 human use biologics approved for use globally since 1990, and Medicines Australia states that more than 900 are currently under development.[79] The number that are 'under development' appear to have more than doubled in the 2011–2012 year, when in March 2011, just over 400 human use biologics were reportedly under development. Internationally, however the number of approved biologics is more stable.[80]

Chart 2.22 illustrates the relative number of new molecular entities approved by the US FDA annually, compared to the number of biologics. It is estimated that the value of biotechnology products (defined as bioengineered vaccines and biologics) as a proportion of the world's top 100 drugs will increase from 11 per cent observed in 2011, to approximately 49 per cent by 2018.[81]

This will be driven by growing demand and availability of biologics, as well as biologics carrying a much higher price tag than traditional medicines — estimates for treatment

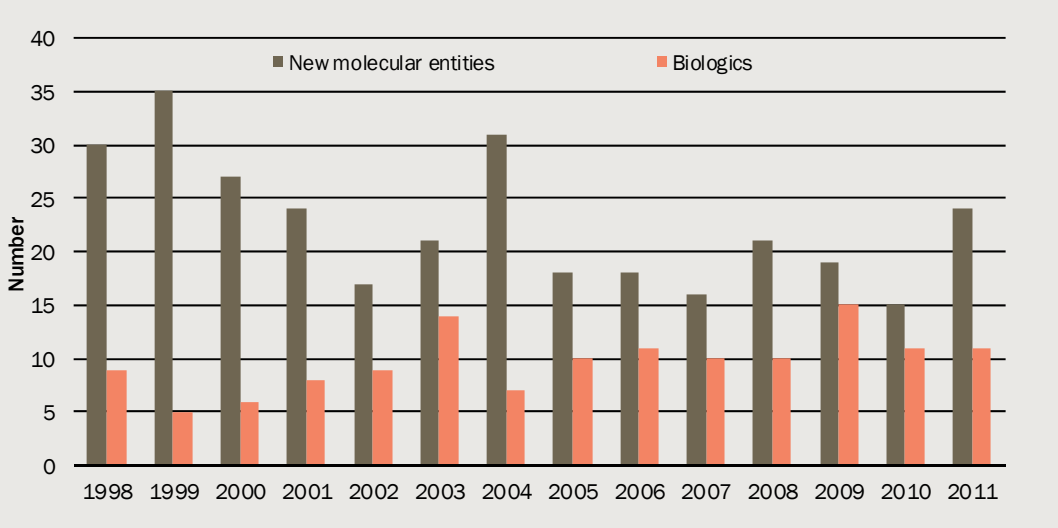
78 International Federation of Pharmaceutical Manufacturers & Associations 2012, Biotherapeutic Medicines — Grasping the New Generation of Treatments.

79 Medicines Australia 2012, *Biologics: a new frontier in treating disease*. Media Release 7 August.

80 Medicines Australia 2011, *Gene Bill threatens access to biologic medicines.* Media Release 1 March.

81 EvaluatePharma 2012, World Preview 2018.

2.22 New molecular entities and biologics approved by the US FDA



Data source: EvaluatePharma (2012) World Preview 2018.

costs in the United Kingdom for biologics are estimated at $14 750 per patient per year, compared with $700 for more conventional medicines).[82]

This reflects the fact that biologics are highly complex and require a great degree of skill and precision during the manufacturing process, more than chemical based medicines.

Where biologics refers to products derived from proteins and substances produced by living organisms, a large portion of the research, especially for human use biologics, rests on the use of recombinant DNA technology. In some cases, whether based on recombinant DNA technology or not, isolated human gene sequences (and associated patents) are also involved.

82 National Institute for Health and Clinical Excellence 2012, Commissioning biologic drugs for the treatment of inflammatory disease in rheumatology, dermatology and gastroenterology.

3 Isolated Human Gene Patenting in Australia

It is estimated that at least 3700 (and likely to be between 3000 and 4400) isolated human gene patents and applications that have ever been filed for in Australia include at least one claim to an isolated human gene sequence.

Detailed analysis of close to 1400 individual patents indicates that all full-length gene sequence patents in the sample[83] were filed prior to the completion of the Human Genome Project (HGP) in 2003. Seventy-four per cent of isolated human full-length gene patents, with a counterpart in nature, ever filed are no longer in force — that is they have expired or ceased.

In terms of actual patent numbers, there is estimated to be at least 456 (and most likely between 284 and 627) isolated human gene patents still in force in Australia today that claim some aspect of an isolated human gene. Only 4.8 per cent of these are held by Australian entities.

Based on this sample, only 24 per cent of all full-length gene sequence patents ever granted in Australia are still in force. Sixty-one per cent of all partial gene sequence ever granted are in force, and only 15 per cent of method only patents ever granted are still in force.

Of those that are still in force, most *do not* have a counterpart in nature or a method-only patents (57per cent) and 43 per cent do. Full-length gene sequence patents are the least in number, comprising 19 per cent of patents still in force, compared to 59per cent for partial and 22 per cent for method-only patents.

What are isolated human gene sequence patents?

Like all patents, there are a wide variety of isolated human gene patents covering many different technologies and methodologies.

Individual researchers and entities are able to make a claim for some aspect of an isolated human gene if they are able to satisfy patentability criteria in the Patents Act 1990.

The purpose of patenting is it to exclude others from making, using or selling the product or process defined by the patents claims unless agreed to by the patent holder. Within a patent application, the applicant must make a set of claims that define the scope of boundaries of protection for the invention. The claims within a granted patent will define the 'monopoly' that the patentee holds.

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83 Isolated human full-length gene sequence patents claim a genetic sequence that encodes a human protein. Within this group of patents, there are those that have a naturally occurring counterpart and those that are derived from a naturally occurring gene sequence and therefore do not correspond to a naturally occurring gene.

Isolated human gene sequence patents are the subset of total gene sequence patents that include at least one claim to an isolated human gene sequence. These claims could be a claim to:

- a full length isolated human gene sequence, that is a gene sequence encoding a human protein;
- a partial isolated human gene sequence, that is a sequence that corresponds only to a portion or fragment of a full length gene, for example, a probe or primer sequence; and
- a modified full or partial isolated human gene sequence, that is a sequence that has been altered in some way from its naturally occurring counterpart, for example, the gene sequence is altered to code for an altered protein with improved properties from the wildtype. These gene sequences do not have a counterpart in nature.[84]

What else is claimed in isolated human gene sequent patents?

Types of isolated human gene patent claims

Isolated human gene sequence patents typically include product claims (referring to the isolated gene sequence itself, either in whole or in part), a method claim (the use of a gene sequence for a therapeutic or diagnostic purpose) or both.[85]

Product claims can include the isolated gene sequence, and claims to various products obtained using the sequence. These products include proteins encoded by the gene sequence and vectors containing the gene sequence used for recombinant expression[86] of the sequence. If an entity holds a patent that covers an isolated human gene sequence, this means that the patent holder can exclude others or require permission for its use of the specific gene sequence and its encoded protein claimed in the patent.

Method claims or 'downstream applications' can be diagnostic and/or therapeutic claims.

- **Diagnostic claims** refer to the use of the gene sequence as a probe or primer for the diagnosis or prognosis of a disorder.
- **Therapeutic claims** describe the use of an isolated gene sequence or encoded protein for the treatment of disease, such as gene therapy.

Method claims prevent other parties from using the gene sequence for the particular purpose claimed in the patent.

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84 Modified full or partial human gene sequence patents are not included in the sample for this study.

85 IP Australia/DIISR, Senate Committee Community Affairs: Inquiry into Gene Patents, Chapter 4.

86 The laboratory process where an artificial gene (recombinant gene) is used to express its encoded protein.

How many isolated human gene patents are there?

A stocktake was performed on isolated human gene patents, (we have included both isolated human gene sequence patents and patent applications). Ungranted applications have yet to be tested for patentability and some applications may have lapsed prior to being granted. Granted patents are either still in force or are no longer in force because they have ceased or expired.

Within this analysis we have categorised patents based on their earliest priority date[87] as this is the date when patentability is assessed. Our analysis of isolated human gene patents in Australia is based on patents that had been examined and granted, and are either still in force, or no longer in force. It does not include analysis of patents that have not been granted.

How many isolated human gene patents and applications are there?

There is no published estimate or repository specifically relating to isolated human gene patents and patent applications in Australia.

Obtaining an estimate of the number of patents and filed applications that claim an isolated human gene sequence is complicated. This is because it is difficult to distinguish patents that claim an isolated sequence product itself from those patents that merely mention or refer to a sequence in the claims. For example, some patents do not claim isolated gene sequences, but rather claim methods of using sequences.

To extrapolate the number of isolated human gene patents, a broad search strategy has been employed to capture the *maximum potential* number of patents and patent applications that claim an isolated human gene sequence.

3.1 Methodology

AusPat[88] was searched using the search terms 'SEQ' and all varieties of the word 'sequence' in conjunction with International Patent Classification (IPC) marks and a set of keywords. IPC marks are assigned to each patent application based on the field of technology that it is in. While there is no discrete IPC mark for isolated human gene patents, and patents are assigned more than one mark, the most relevant classes of IPC mark include C12,CO7K and CO7H. C12N covers inventions within the genetic engineering space relating to DNA and RNA.[89] CO7K relates to proteins and peptides and may cover patents that claim a genetic sequence that encodes a protein. It is likely that gene patents relating to isolated human genes are within these marks. See Appendix A for more information on the patent search methodology and the sampling methods utilised for the sample analysis.

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87 The earliest priority date refers to the earliest filing date and it is this date when patentability is assessed (novelty and inventive step). This will differ to the filing date when an applicant files in another country and uses that date as the priority date, or when a provisional application is filed.

88 AusPat is the repository for all patents and patent applications in Australia. http://pericles.ipaustralia.gov.au/ols/auspat/

Based on the approach described in box 3.1, we estimate that there have been 54 306 applications that have text in them mentioning 'sequence' and some relevant technology term. These applications may just mention these terms in their abstract, may claim a product or method related to gene technology but not a gene, and may claim non-human genes.

In order to assess the nature and type of isolated human gene patents, and changes in patent activity over time, randomised sampling of the data set was performed to ring-fence a subset of patents that could be subject to scrutiny. Analysis included reviewing the patent claims in particular, including the abstract and background information.

The sample of identified isolated human gene patents were classified according to descriptors explained in appendix E.1 to analyse types of isolated human gene patents in Australia.

To obtain an estimate of the total number of isolated human gene patents in the set of patents identified through the different search strategies, the sample estimate was extrapolated in a number of ways.

- By search strategy — the incidence of isolated human gene patents in each search strategy was extrapolated to the number of patents identified by that search strategy and then these were combined to give a total estimate of isolated human gene patents.
- By search strategy and year — in addition to search strategy, differences across incidence rates by year were allowed for.[90]
- By search strategy and year jointly — differences were allowed for in incidence rates for each search strategy and year combination.[91]

The estimated number of patents was similar for the different methods, as shown in table 3.2. For the first two methods standard errors have also been calculated. The estimated number of patents for a randomly drawn sample should approach a normal distribution.

3.2 Isolated human gene patents and applications ever filed under different extrapolation methods

Method	With a counterpart in nature	Without a counterpart in nature	Total
	No.	No.	No.
Search strategy	2 502	1 198	3 700
Search strategy and year	2 535	1 249	3 784
Search strategy and year jointly	2 446	1 103	3 550

Source: The CIE.

89 A gene is a discrete segment of DNA that carries information for the amino acid sequence of a protein. A nucleic acid is a molecule composed of nucleotide subunits such as DNA or RNA. DNA (Deoxyribonucleic acid) carries genetic information and is a double stranded polymer. RNA (Ribonucleic acid) is a single stranded nucleic acid molecule and mRNA (messenger RNA) is transcribed from DNA and is the template for protein synthesis.

90 Formally, allowing for a common factor by year (C_Y) and a common factor by search strategy (C_S).

91 Formally, allowing for a factor that is different for each year and search strategy combination ($C_{Y,S}$).

Hence, there is a 95 per cent statistical confidence that the actual number of patents from these search strategies is within ± 2 standard errors.

The results of this analysis are summarised in table 3.3. This indicates that the estimated number of isolated human gene patents and applications from the search strategies employed is likely to be in the range of 3000 to 4400.

3.3 Estimate of the total number of isolated human gene patents ever filed in Australia

Item	Patents with a counterpart in nature		Patents without a counterpart in nature		Total isolated human gene patents	
	Estimate	Standard error	Estimate	Standard error	Estimate	Standard error
Extrapolation by search strategy [a]	2 502	275	1 198	228	3 700	350
	Results at the 95 per cent confidence interval for total isolated human gene patents — 3000 to 4399					
Search #1	1 249	96	447	65	1 696	103
Search #2	1 108	236	317	129	1 425	265
Search #3	145	102	1 198	228	3 700	350

[a] The total standard error is calculated on the basis that patent incidence for each search strategy is normally distributed and independent of other search strategies, which would be expected from random sampling. Figures do not add up due to rounding issues in STATA.
Note: Standard errors are calculated as the standard deviation of the sample divided by the square root of the number of sample observations minus 1.
Source: The CIE.

This includes patents and applications over genomic DNA that are claimed and exemplified, genomic DNA that are claimed and not exemplified (which comprise patents with a counterpart in nature), and cDNA and partial sequence claims (which for the purpose of this study comprise patents without a counterpart in nature).

The results shown exclude patents over modified DNA, modified antibodies, and method only claims, which were not the focus of the patent search strategy, and the sampling methodology was deemed insufficient to properly represent these patent types. For instance, there are expected to be a much larger number of method-only isolated human gene patents, but given they do not claim any part of an isolated gene sequence, the search strategy for this study was not designed to fully capture them, as they are not relevant for counting patents or applications that claim an isolated human gene patent *per se*. [92]

The statistical confidence intervals noted in the table above reflect confidence in the estimate of the number of isolated human gene patents and applications for the patent types identified by the search strategies.

In the case of method only patents, those patents that were incidentally identified as part of the gene sequence search are included in the analysis that follows, as they are an area

92 This includes patents over genomic DNA that are claimed and exemplified, genomic DNA that are claimed and not exemplified, cDNA, and partial sequence claims. This excludes patents over modified DNA, modified antibodies, and method only claims, which were not the focus of the patent search strategy and the sampling methodology was deemed insufficient to properly represent these patent types. A select, although broad, number of IPC marks were used in the search strategy.

of interest for this study. This is not the case for modified, or modified antibody patents which are excluded from this study.[93]

Profile of isolated human gene patents ever granted in Australia

Different types of isolated human gene sequence patents

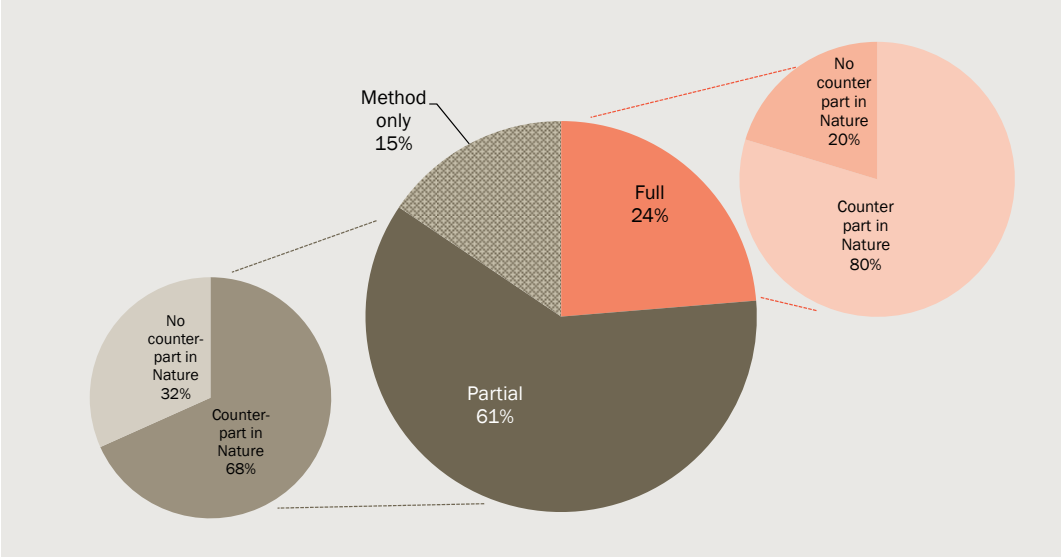
Before focussing specifically on patents in force today, it is important to understand the history of patenting activity in Australia, and to see how patenting activity has changed. Hence, the analysis immediately below reflects an assessment of the full sample of granted isolated human gene patents, including those that are no longer in force. [94]

It also distinguishes between a gene sequence product that claims a full or partial gene sequence, and patents that include method-only claims. This is important as the type of sequence claimed, and the type of method claimed, have different effects on the exclusions to other entities.

Chart 3.4 shows that 24 per cent of isolated human gene patents ever granted in Australia described full-length genetic sequences (a gene sequence determining a protein such as an enzyme or structural protein). More than half of the gene patents (61 per cent) claim partial gene sequence and 15 per cent have only method of use claims.

Chart 3.4 also shows the breakdown of full-length gene sequence patents that have a counterpart in nature (80 per cent) and those without a counterpart in nature (20 per cent).

3.4 Distribution of all isolated human gene patents ever granted in Australia



Note: Random sample includes 270 observations.
Data Source: The CIE.

93 The search strategy for this study was developed and approved by IP Australia.

94 To analyse isolated human gene patents in detail, 983 patents were individually examined and classified , of these, 165 were identified as granted isolated human gene sequence patents. Further, a sample of 410 patents were examined and classified, 105 of these were identified as granted isolated human gene sequence patents.

An example of a typical full-length gene sequence patent includes a patent which claims a kinase interacting protein.[95]

Patents that claim a partial gene sequence generally claim the use of the sequence as a probe or primer for diagnostic or therapeutic purposes. An example of a partial gene sequence patent is a DNA fragment.[96] Sixty-eight per cent of partial gene sequence patents ever filed in Australia have a counterpart in nature, and 32 per cent without.

Method (or use) only patents do not claim a gene sequence, but instead claim a use for the sequence. An example of a method only patent includes a patent that aims to use identified genes to predict a patient's responsiveness to a certain drug.[97]

The analysis of patents include only granted patents. A patent that is 'Granted' is in force and those that are no longer in force refer to patents that have expired, ceased or have been revoked (see table 3.5 for status terms).

3.5 Definition of patent in Australia status terms

Terminology	Meaning	Granted patent
In force		
Granted	Once a patent application has been granted, the file is sealed and is still in force	✓
No longer in force		
Expired	A granted patent has lived its full term of protection	✓
Ceased	Occurs when renewal fees are not paid or prescribed documents are not sent for a granted patent	✓
Revoked	A granted patent has been terminated	✓

Data source: The CIE

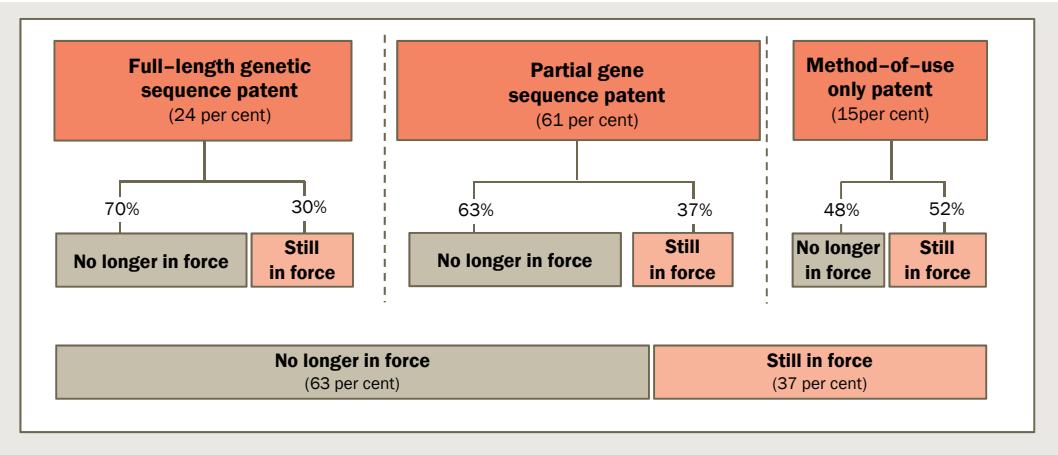
Chart 3.6 illustrates the magnitude of inactive patents. Only 37 per cent of all patents ever filed in Australia are still in force. The 63 per cent of patents are no longer in force (expired, ceased or revoked). Based on the sample, only 30 per cent of all full-length gene sequence patents ever filed in Australia are still in force. Only 37 per cent of all partial gene sequence are in force.

95 AU 764094 B2, 'MEKK1 (serine threonine kinases)-interacting FHA (forkhead associated domain) protein 1 (MIF 1)', this patent has ceased.

96 AU 666689 B2, 'DNA fragment which codes for tumor cell proliferation inhibiting factor', this patent has ceased.

97 AU2005250142 B2 'Biomarkers for the prediction of responsiveness to clozapine treatment', this patent is granted.

3.6 Status overview of isolated human gene patents ever granted in Australia



Note: This chart is not to scale and for illustrative purposes only. Random sample includes 270 observations.

Data source: The CIE.

Gene sequences with and without a counterpart in nature

Some of the controversy surrounding isolated human gene patents is based on the distinction between patents and patent applications that correspond exactly to naturally occurring genes, and those that are modified from naturally occurring gene sequences. The latter group of patents do not claim a gene sequence that has a counterpart in nature, and includes cDNAs and claims to only a partial sequence that would not exist in nature.

It is important to distinguish between whether the claimed gene sequence has a counterpart in nature or does not. Table 3.7 provides definitions of claim types relating to counterparts in nature. Patents and applications that claim a method of use only do not claim an isolated gene sequence and hence are not a part of this analysis.

Patents with a counterpart in nature have claims explicitly describing a length of isolated human DNA, specifically a length of genomic DNA. Within the group of patents that claim a gene sequence with a counterpart in nature there are two distinctions. Patents that claim and exemplify a genomic DNA (gDNA), and those that claim but do not exemplify a gDNA. The latter group refer to patents and applications that do not isolate or disclose a gDNA sequence, but given the broadest interpretation of claims, also cover the gDNA sequence as well. The significance of this is that in some cases an applicant may have to narrow their claims to cover only the cDNA sequence after initial examination by IP Australia.

3.7 Definitions of gene sequence claim types

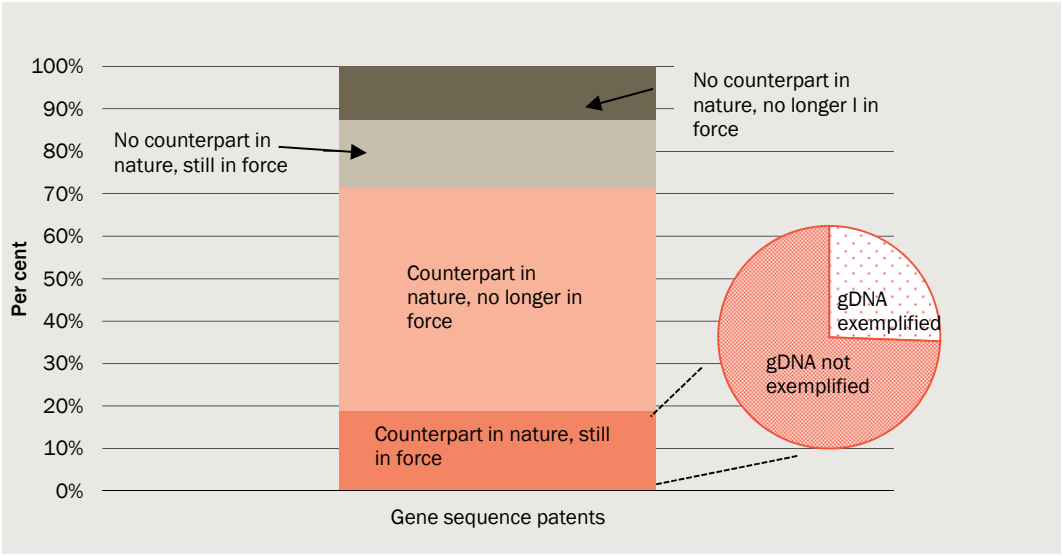
Type	Description
Counterpart in nature:	
Genomic DNA claimed and exemplified	Genomic clone has been isolated and the sequence of the gDNA is disclosed and claimed.[98]
Genomic DNA claimed but not exemplified	The genomic clone has not been isolated and only the cDNA sequence has been determined. However, there is a claim in the claim set that is construed/interpreted as covering the genomic clone as well as the cDNA. [99]
No counterpart in nature:	
Complimentary DNA sequence	Complimentary DNA (cDNA) is the laboratory made version of a gene sequence and does not include the introns found in gDNA, hence, cDNA does not have a counterpart in nature.
Partial only	Claims to probe/primers and fragments or segments of polynucleotide sequences. Fragments such as these would not exist in nature.

Note: For the purposes of this study we have not included modified gene sequences in the analysis. Modified gene sequences refer to modified polynucleotide sequences to make modified proteins, and would not have a counterpart in nature.

Source: The CIE.

Chart 3.8 illustrates that more than half of patents ever granted that claim an isolated human gene sequence (not method only patents) actually claim a sequence that has a counterpart in nature (71 per cent). Of the patents that do claim a sequence with a counterpart in nature 74 per cent are no longer in force. The patents that are still in force that claim a sequence with a counterpart in nature are split between those that claim and exemplify a gDNA sequence (26 per cent) and those that do not exemplify the gDNA (74 per cent).

3.8 Status analysis of isolated human gene sequence patents



Note: Method only patents were not included in this chart. Total observations 228.

Data source: The CIE

98 AU 2000061764 B2, 'Prostate cancer-released gene 3 (PG-3) and biallelic markers thereof, this patent has ceased.

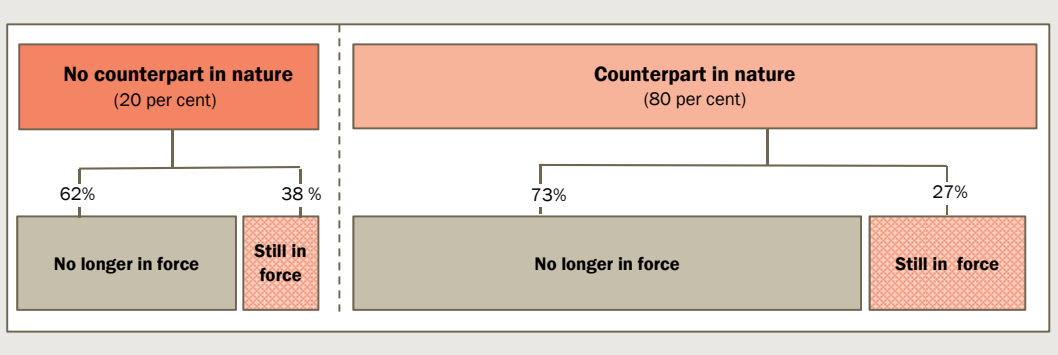
99 AU 757749 B2, 'Isolated DNA encoding human H3 histamine receptor'.

Chart 3.9 shows that of the sampled full-length sequence patents ever applied for in Australia, 20 per cent described a genetic sequence that was *derived* from nature (no counterpart in nature). Of the full-length patents with no counterpart in nature, 38 per cent are still in force.

The majority of full-length gene sequence patents that have a counterpart in nature patents are no longer in force (73 per cent).

Chart 3.10 examines the status and claim types of isolated human partial gene sequence patents. More than half (68 per cent) of the claim types for partial sequence patents are over sequences with a counterpart in nature. However, only 26 per cent of these are still in force. Sixty per cent of isolated human partial gene sequence patents that do not have a counterpart in nature are still in force.

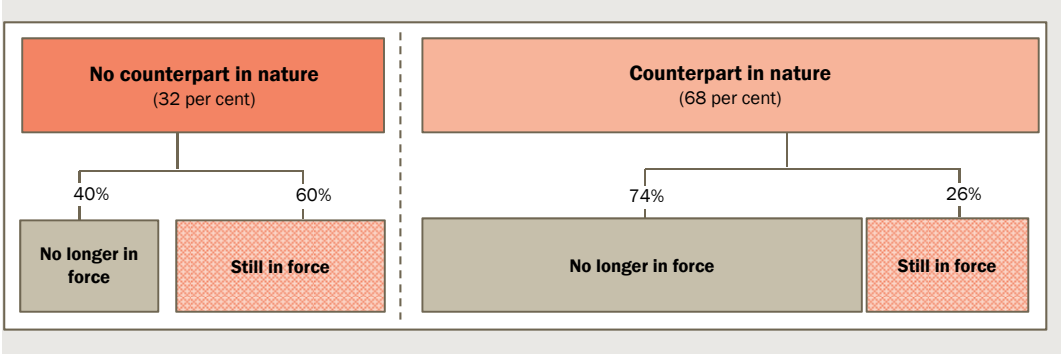
3.9 Full–length sequence isolated human gene patents with/without a counterpart in nature



Note: This chart is not to scale and for illustrative purposes only. Total observations 64.

Data source: The CIE.

3.10 Partial gene sequence isolated human gene patents with/without a counterpart in nature



Note: This chart is not to scale and for illustrative purposes only. Total observations 164.

Data source: The CIE.

Isolated human gene patents today: a profile of current patents

Status of isolated human gene patents and patent applications

Granted patents or patent applications may either be active or inactive. Patent applications must go through examination by IP Australia and can be granted, or refused.

The applicant may also withdraw their application or allow it to lapse if they do not address patentability criteria. Granted patents that are sealed are known as being 'still in force', however they are no longer in force if they expire or cease.[100] An analysis of patents by status has been undertaken to assess the contemporary nature of isolated human gene patents, and to observe how patents have changed over time.

Gene patents still in force

A patent application that passes the test of patentability is granted. This patent is *in force* and the patentee can exclude others from the use of the invention or require permission for its use. Patent applications can be listed as filed and are under review, or accepted and therefore waiting for patent status to be granted.

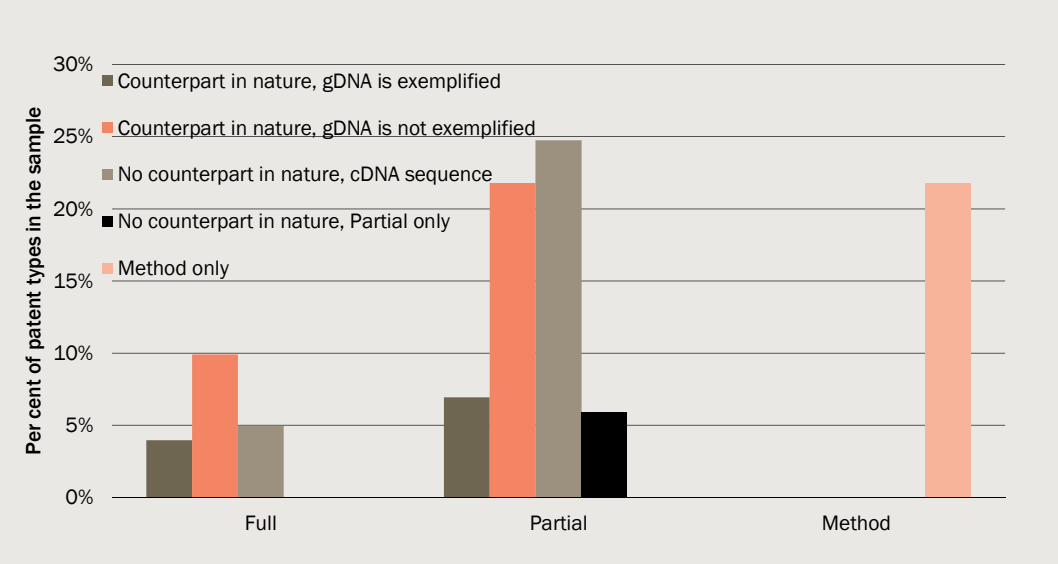
There are 456 isolated human gene sequence patents estimated to be in force today. At the 95 per cent confidence interval, there are between 284 and 627 isolated human gene sequence patents in force.

Based on the sample of scrutinised patents, there are 37 per cent with a counterpart in nature and 63 per cent without a counterpart in nature that are still in force. Of particular significance is the relatively small number of full-length gene sequence patents. Full length gene sequence patents comprise 19 per cent of patents still in force, compared to 59 per cent for partial and 22 per cent for method only patents.

Chart 3.11 shows the type of full, partial and method only isolated human gene patents that are still in force as of 2012. Most (74 per cent) of isolated human full length gene sequence patents that are still in force do have a counterpart in nature. Only 4 per cent (full-length gene sequences) and 7 per cent (partial gene sequences) of total sampled patents that are still in force claim and exemplify a gDNA sequence. Around half of the patents still in force have claims over a gene sequence with a counterpart in nature (43 per cent) and without (57 per cent).

100 Applicants may choose not to pay renewal fees for a granted patent when they believe that it is not worth the cost, that is, commercialisation of the technology is too difficult, the market is not big enough or it may be too difficult to put the technology into practice. Therefore, not all granted patents live their whole term (normally 20 years) until expiration, these patents are listed as ceased.

3.11 Patents still in force today based on claims



Note: Total observations 79.

Data source: The CIE.

Expiries in gene sequence patents

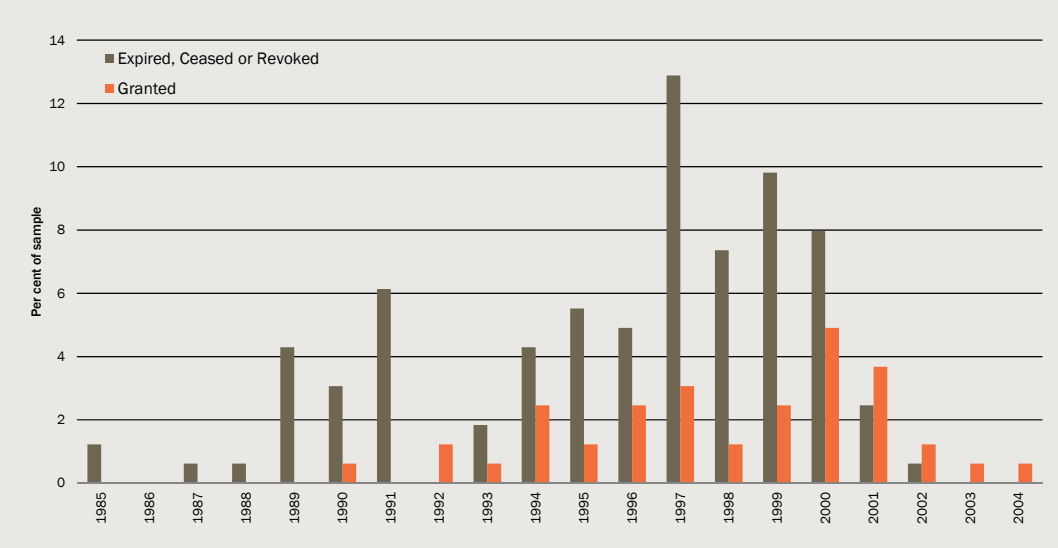
The gradual expiry and withdrawal of patents over time has a notable impact on the profile of isolated human gene patents and applications in Australia that are in force today.

Patents with a counterpart in nature

Based on analysis of the randomly sampled gene sequence patents with a counterpart in nature, Chart 3.12 shows that the majority of these patents have either expired, ceased, or been revoked, (74 per cent). In particular, of these granted patents no longer in force 95 per cent were ceased, meaning that they were not held for their fully available term.

The remaining counterpart in nature gene patents that are still in force (26 per cent), have priority dates as early as 1990 indicating that these inventions will soon come off patent assuming renewal fees are paid and the term for a standard patent of 20 years is applied.

3.12 Status of counterpart in nature gene sequence patents in Australia



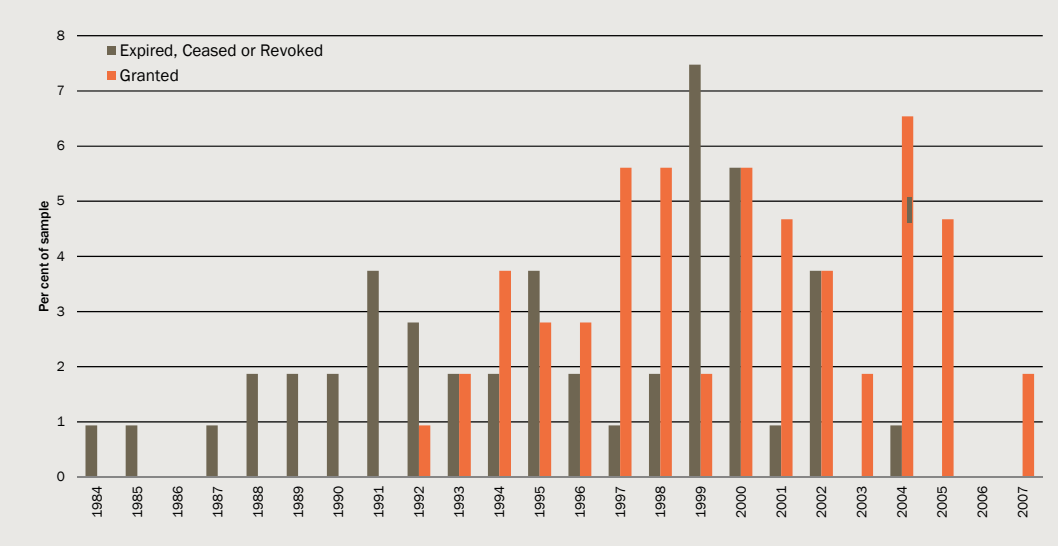
Note: Total observations 163.

Data source: The CIE.

Gene patents with no counterpart in nature or method only claims

Most of the gene patents are towards sequences that have no counterpart in nature, or only claim a method of using a sequence (40 per cent). Chart 3.13 shows almost half of these patents are no longer in force (46 per cent), with the remaining still in force (54 per cent). Chart 3.12 and 3.13 include both full-length and partial gene sequence patents. Interestingly, chart 3.12 shows that the majority of ceasing of patents occurred in patents with earliest priority date between the years 1997 and 2003. Both chart 3.12 and 3.13 show their highest peak of patents no longer in occurring before 2001, the year that the first draft of the HGP was published.

3.13 Status of no counterpart in nature gene sequence patents or method only patents



Note: Total observations 107.

Data source: The CIE.

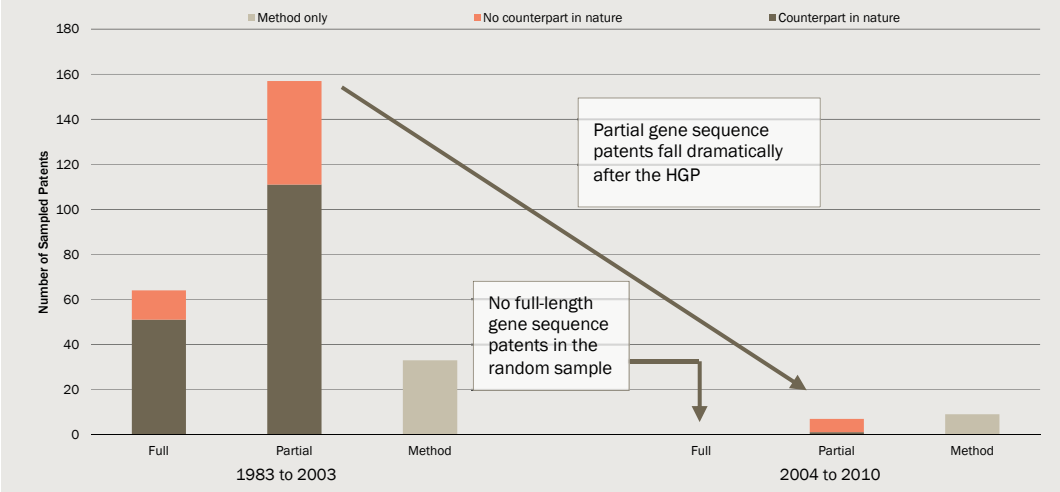
The effect of the Human Genome Project

The HGP and its successors have had an important impact on information surrounding the human genome. Since its inception, it has become increasingly difficult for a claim to an isolated human gene sequence to satisfy patentability requirements for novelty and considered with other developments in the field of biotechnology on inventive step. The patent market has responded with an increased tendency towards downstream applications of method of use claims over therapeutic and/or diagnostic methods.

Whether or not the invention under patent application meets both the novelty and the inventive step requirements, patentability is examined using the priority date, which could be many years in the past.[101] Patents in the random sample constructed for this study were sorted into those with a priority date up to, and including 2003, and from 2004 onwards. This was undertaken to determine the changes in patents since the HGP.

Chart 3.14 indicates that 94 per cent of the sampled gene sequence patents had an earliest priority date prior to and during 2003. This is of particular significance as it indicates the effect the HGP had on patent applications regarding novelty. From the random sample, there were no full-length gene sequence patents with priority dates post 2003. There is a smaller percentage of sampled patents with priority dates after 2003 as this study only focused on examined and granted patents. The process of an application being examined and either granted or refused can take several years, hence, the lack of granted patents in the sample after 2007.

3.14 Overview of the types of isolated human gene patents pre and post the completion of the Human Genome Project



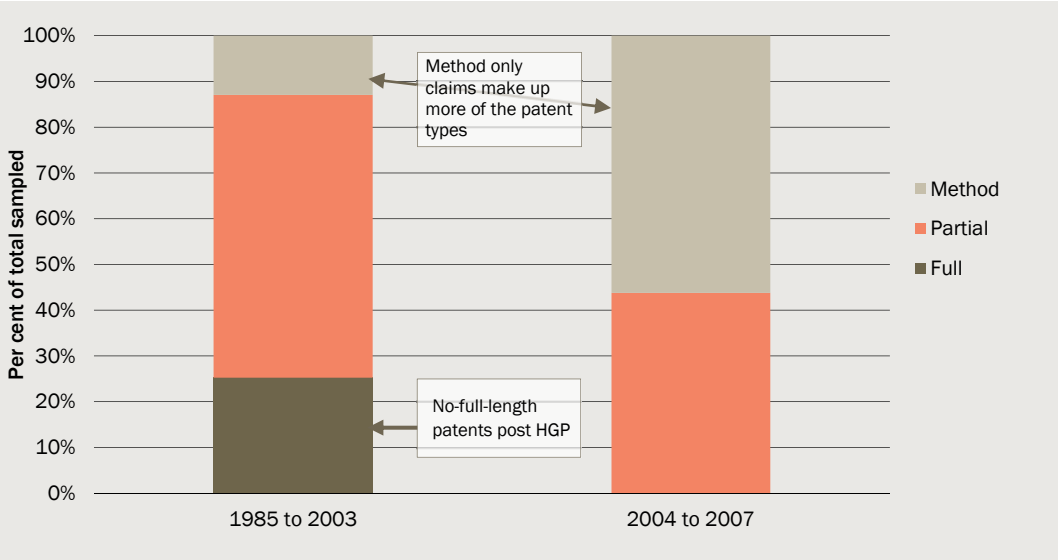
Note: Random sample included 270 observations.

Data source: The CIE.

101 A patent application establishes the priority date of an invention, it is at this date that the patentability criteria such as inventiveness and novelty are assessed. The patent examination process takes time, sometimes years. Another reason for a time delay is when a company, say in the U.S decides to apply for a patent in another country/jurisdiction, for example, in Australia. After filing a PCT application (Patent Cooperation Treaty, a vehicle used for international patent applications), an Australian application is filed. The application is examined by IP Australia who would base the patentability criteria on the priority date, which is the date of the first filing in the U.S.

Chart 3.15 explores the different types of patents before and after the completion of the HGP. Of most significance is the drop in partial sequence patents, which fell from 62 per cent pre 2003 to 44 per cent post 2003. The proportion of patents with method-only claims increased due to the drop in sequence patents from 13 per cent to 56 per cent after the completion of the HGP.

3.15 Types of patents pre and post the completion of the Human Genome Project



Note: Random sample included 270 observations.

Data source: The CIE.

Spectrum of applicants

The biotechnology industry is very competitive and patents are considered necessary to protect inventions. However, there are factors subsequent to the issuing of a patent that affect whether an invention is translated into a therapeutic or diagnostic tool. For example, a company is likely to require patent protection to attract and obtain investments and funds for clinical trials (this is to ensure that the technology, whether it is a recombinant protein, a monoclonal antibody or a diagnostic kit actually works in patients). The cost for such trials is high (see chapter 4), partly attributed to the relatively high attrition rate for therapeutics leaving the pipeline (therapeutics that a company is working on at varying stages)[102].

In reality, not all patented inventions actually produce a marketable product, which is reflected in the high lapse rate of applications, and the cessation rate of granted patents. Furthermore, the nature of a patent is that protection is granted on the basis that the holder publishes the invention for the public to see. Once a patent is no longer in force, the invention is free to be used (researched) by anyone, adding to the pool of scientific knowledge available.

102 DiMasi, J, A, Grabowski, H.G, 'The cost of biopharmaceutical R&D: Is biotech different?', 2007, Managerial and Decision Economics, 28, pp. 469–479.

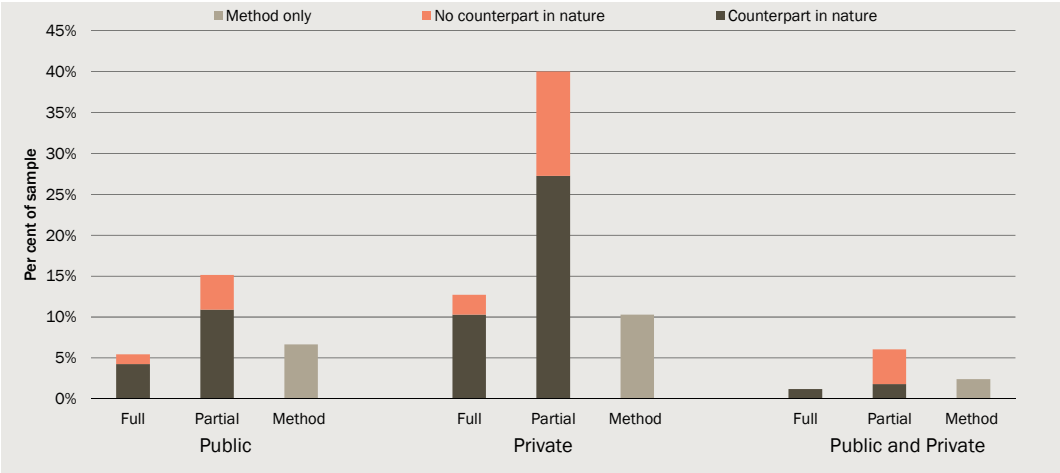
Public and private applicants

The majority of applications for patents are from private companies, defined as a biotechnology, pharmaceutical and/or diagnostic company. All other types of applicants were classified as public organisations, for example, universities, government, medical research institutes and hospitals. Chart 3.16 highlights the sampled patents held by only private entities made up a significant portion of the sample (63 per cent).[103]

A small portion of patents was applied for by a joint private and public initiative (9.7 per cent). Collaborations between academia and biotechnology companies do occur, and this can result in joint patent applications. In these cases, the costs associated with patent filing and maintenance are shared by the applicants. This can reduce the financial burden for a medical research institute.

This high level of private representation reflects the fact that private corporations mainly perform patent filing as a means to protect their invention and promote investment. Furthermore, it is more likely that these companies will translate the invention into a product or service that will treat people as this is their major goal.

3.16 Public and private applicants of isolated human gene patents



Note: This analysis utilised a subset of the random sample due to the descriptor information available, total observations is 165.

Data source: The CIE.

Full-length gene sequence patents filed by private companies

Most full-length gene sequence patents are held by private companies only — biotechnology, pharmaceutical corporations, or diagnostic companies without any joint ownership with a public applicant such as medical research institutes, government organisations, universities and hospitals.

Private corporations applied for most of the full sequence gene patents (66 per cent), however, it should be noted that 86 per cent of these are no longer in force.

103 The Spectrum of Applicants analysis is based on a subset of the sample used in the previous analysis as the categorisation of these patents included applicant descriptors, n=165.

Domestic and international applicant trends

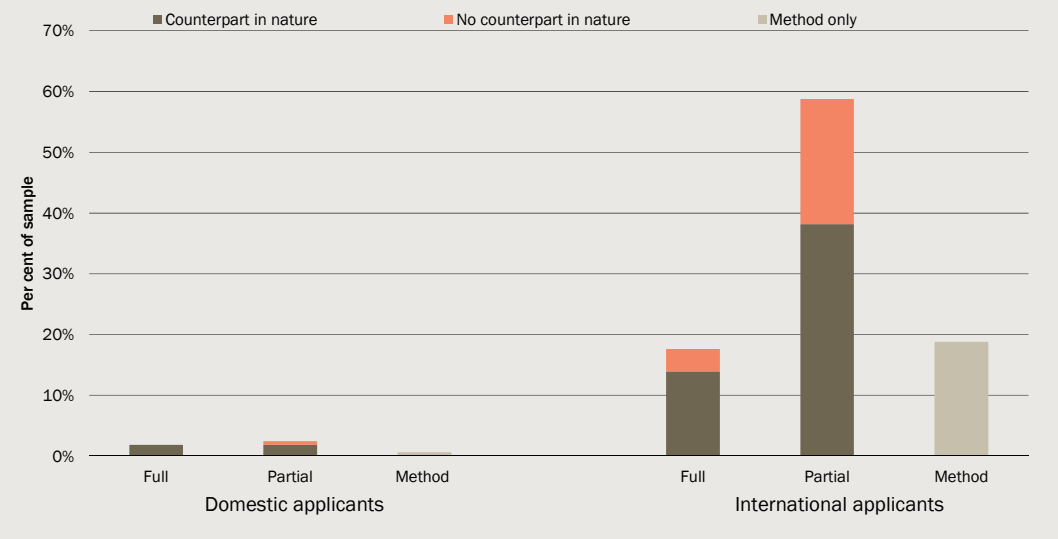
The majority of patents in Australia are being applied for by overseas applicants — only 4.8 per cent of sampled patents have Australian patent holders.

The market for the biotechnology and biopharmaceutical industry is global; in particular, the market is much bigger in the US compared to Australia. Patent protection is generally only sought in Australia if an international company decides to market their potential therapeutic use here. For example, if 'Company A' invents a therapeutic method relating to a gene and patents it in the United States and Canada only, then 'Company B' is able to produce that same technology and market it in Japan. Patents only protect an invention in a certain jurisdiction. Hence, most companies will apply for patents in multiple jurisdictions, predominantly the US, UK, Japan, Germany and Canada to name a few. This translates to patent costs for filing, maintaining and defending (if applicable) patents in multiple countries.

Not surprisingly, 219 of the sampled patents (70 per cent) had at least one applicant from the United States (US). Interestingly, some patents had applicants from more than one country, with some US patents including applicants from at least six other countries. This reflects the international scope of scientific research. A further trend emerging is that within these patents there are both public and private companies collaborating with each other. These findings reflect the difficulty of scientific research and the need for collaboration.

Of the 11 sampled Australian applicant patents as shown in chart 3.17, three have full-length gene sequence claims, four claim a partial sequence and one only claims a method of use. Within the sample there are two Australian held patents still in force with only one of these having a counterpart in nature, specifically, claiming and exemplifying a genomic DNA sequence.

3.17 Domestic and International applicants of isolated human gene patents



Note: This analysis utilised a subset of the random sample due to the descriptor information available, total observations is 165.

Data source: The CIE.

4 What it takes: the economics of the business of bringing an idea to market

The IPR regime surrounding patents for DNA based molecules including isolated human gene sequences recognises that the cost and process of getting biologic medicines and treatments to market is considerable.

Research and development costs are around US$1.4–US$1.9 billion per new molecular entity. Lead times from successful research outcomes to regulatory product approval are extensive, with around 10 to 12 years to get a new product to market.

Risks and uncertainties produce high failure rates with only 1 per cent of lead compounds for new targets providing a return on investment. Approximately 30 per cent of all drugs entering clinical testing will reach the market. Hence, an estimated 70 per cent of expenditure per successful drug is spent on failed projects and is therefore a 'sunk' unrecoverable cost.

Given the critical role of private capital in converting innovations into new treatments and medicines, incentivising private investment in gene based translational innovation and development is essential to realising the benefits of more targeted treatments and medical breakthroughs to improve population health.

Patents are one of the key enticements that currently underpins most commercially funded innovation and development in biopharmaceuticals and gene based therapies and diagnostics — although Australia is a small player on the international patent market.

The cost and risks involved in medical research and product development are considerable. Often considerable public and private investment in basic medical research and early stage commercialisation is required, followed by large-scale investment by (typically) multinational pharmaceutical and well-funded biotechnology firms to translate research outcomes into new treatments, medicines and vaccines. In most cases, innovation and development is entirely contingent on the patent regime, or is ignited or predicated on the existence of patented research.

Either way, the financial viability of new drug and biopharmaceutical development depends on the expected costs of, as well as the returns to, R&D.

The process of early stage R&D was covered previously in chapter 2, which identified a range of public and private funding sources for research in Australia, and the research entities involved in delivering research in the human genetics area. This chapter focuses specifically on the downstream process of bringing new innovations to market, through new approved therapeutics and treatments. Typically, these would be underpinned by patents over modified or recombinant DNA technologies, but may also, or alternatively, be underpinned by an isolated human gene patent.

Who brings biopharmaceuticals and diagnostics to market?

In most cases, medicines and diagnostics that are underpinned by a modified isolated human gene patent, or in some cases an isolated human gene sequence patent will be brought to market by global biotechnology and pharmaceutical companies, often in partnership.[104]

In some cases, these companies are based in Australia, and/or may hold an isolated human gene patent granted in Australia. Therapeutic products that are relevant to isolated human gene patents would fall under the broad term of 'biologics' (box 4.1).

In the earliest days of isolated human gene related product development, it was emerging biotechnology companies that started the process of bringing products to market. This likely started around 1973, when Stanley Cohen of Stanford University and Herbert Boyer of the University of California, patented methods for cloning and expressing recombinant DNA. With the help of venture capital funding, Boyer founded Genentech to build a business and develop drugs based on this new innovation.[105]

At the time, Genentech was characteristic of biotechnology companies involved in isolated human gene based product development — that being said, they were a small, relatively young company focused on the innovation of large molecule protein therapeutics. At the time, pharmaceutical companies were generally thought of as large, fully integrated enterprises that relied on medicinal chemistry to innovate, refine, and develop small molecule drugs.

Over the last two decades, the business model of pharmaceutical and biotechnology companies has changed as pharmaceutical companies face the major strategic issue of how best to acquire access to ever-important technologies relating to human gene based research.

Indeed, over time, the distinction between biotechnology and pharmaceutical companies has blurred and both are now directly involved in bringing isolated human gene related products to market.

Some pharmaceutical companies have developed expertise in a highly specific genetic field, as evidenced by Eli Lilly when it entered a contract with Genentech and university researchers at Berkeley to acquire access to the new recombinant technology for insulin in the late 1970s. Similarly, US Merck and Co Merck contracted William Rutter at the University of California to produce the first recombinant vaccine, Recomivax for Hepatitis B, which was approved by the US FDA in 1986.[106]

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104 It is understood, some diagnostic kits are the result of research by public or private pathology laboratories. No information is available about this activity, so the analysis is limited to the main deliverers of biopharmaceuticals and diagnostics, which are biotechnology and pharmaceutical firms.

105 BIO Ventures for Global Health (2012), Biotechnology: Bringing Innovation to Neglected Diseases Research and Development, California, United States, p. 17.

106 Ibid, p. 14.

4.1 Understanding biologics

In practice, the term biologics includes a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins. The term biopharmaceuticals is used below, which are a subset of biologics.

A biologic is manufactured in a living system such as a microorganism, or plant or animal cells. Most biologics are large, highly complex proteins or mixtures of molecules.

In contrast, a traditional pharmaceutical drug is typically small, relatively simple molecules manufactured through chemical synthesis, which means that it is made by combining specific chemical ingredients in an ordered process.

Traditional drugs generally have well-defined chemical structures, and a finished drug can usually be analysed to determine all its various components. By contrast, it is difficult, and sometimes impossible, to characterise a complex biologic by testing methods available in the laboratory, and some of the components of a finished biologic may be unknown.

Biologic products that would be underpinned by an isolated human gene patent (usually over a modified gene sequence but in limited cases over an isolated human gene sequence) would be those that include recombinant proteins, antibody technologies, gene therapies and diagnostic kits containing antibodies or DNA or protein probes and primers. This would include diagnostic tests that are useful for predicting a patient's response to a particular drug treatment based on the patient's genotype,

Source: Derived from BIO Ventures for Global Health (2012), Biotechnology: Bringing Innovation to Neglected Diseases Research and Development, California, United States.

Pharmaceutical companies have also built or acquired general capabilities in human genetics research through licencing and equity relationships with emerging biotechnology companies. Examples include Roche's purchase of 60 per cent of Genentech in 1990, American Home Products (now integrated into Pfizer's) purchase of American Cyanamid in 1994, and various alliances that have been formed with biopharmaceutical companies with a targeted technology.[107]

There is relatively little information on the providers of biotechnology diagnostics and biopharmaceuticals. The closest data source on types of biotechnology developers relates to public and private sectors participating in neglected disease vaccine development, albeit an imperfect comparator.[108]

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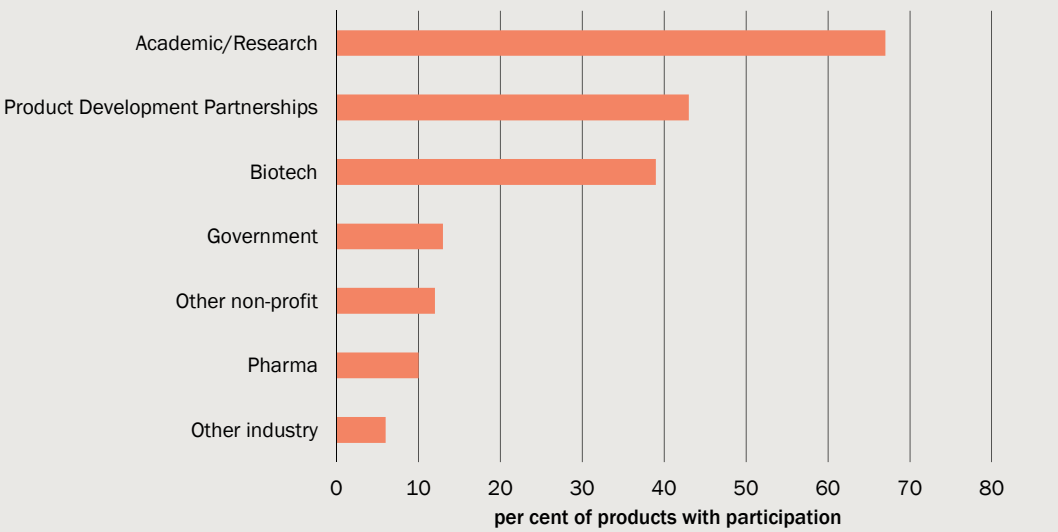
107 Ibid, p. 14.

108 While vaccines can be considered as biopharmaceuticals, it is acknowledged that the development models between vaccines and pharmaceuticals and diagnostics may not be well aligned. Biopharmaceuticals is a large industry and can rely on gene technology including pharmacogenetics (personalised medicine where some aspect of a drugs' suitability relies on the genetic makeup of a patient) and recombinant proteins (for example, recombinant insulin).

Chart 4.2 shows academic and research institutions have the highest level of participation in product development (52 per cent), followed by government (41 per cent), biotechnology companies (40 per cent) and product development partnerships (40 per cent). Pharmaceutical company participation is much lower in vaccine development than drug development (10 per cent as compared to 28 per cent for drugs), while government participation is much greater (41 per cent as compared to 17 per cent for drugs).

4.2 Participation by developer type for neglected disease vaccines in development



Note: Diseases include HIV, tuberculosis and malaria. In many cases there are multiple parties involved, hence percentages do not add to 100.

Data source: Bio Ventures for Global Health 2012, *Global Health Primer 2012 Snapshot*, August, p. 8.

How is it done?

In the early stages of R&D, biotechnology or pharmaceutical companies will screen for chemical or biological compounds that exhibit the potential for treating new or existing conditions. For any particular medicine, researchers identify a promising compound among the 5000–10 000 screened, on average.

Researchers extensively test the compound to ensure its efficacy and safety, which itself can take 10–15 years.[109] In 2011, 35 new medicines were launched in the US, while more than 3200 compounds were at different stages of development, indicating the many research hurdles that need to be overcome before compounds can be developed into safe and effective medicines.[110]

Chart 4.3 provides a high-level overview of the R&D process with key phases in development that eventually lead to one marketed medicine. Patent applications are typically a matter of course prior to clinical testing.

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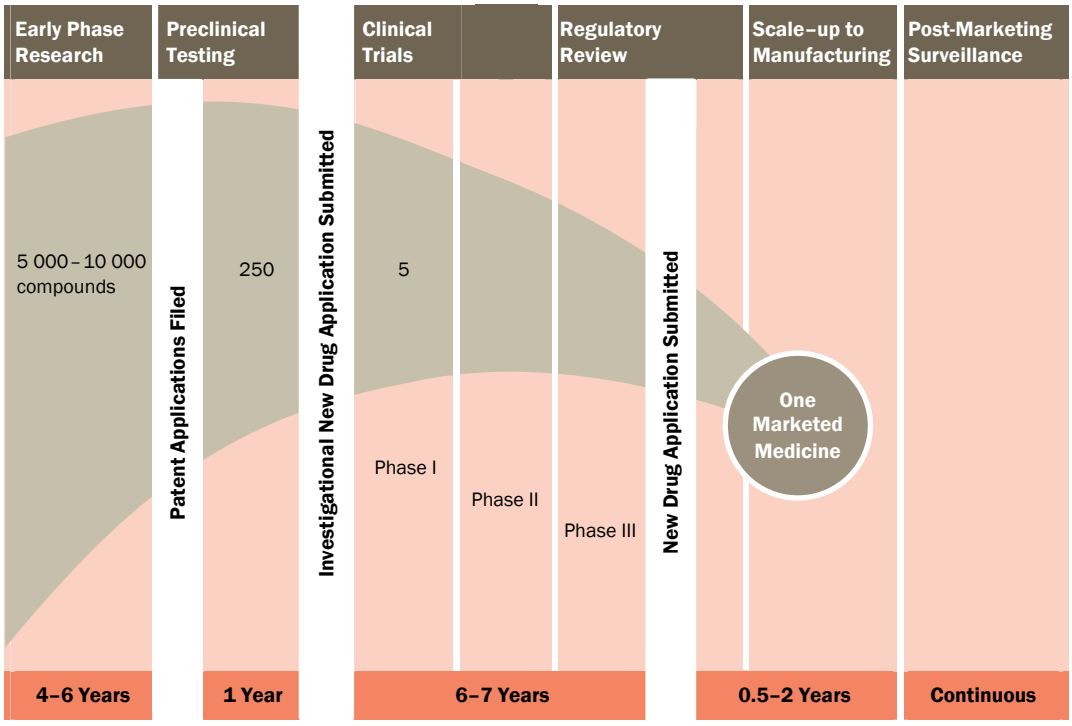
109 Innovation.org (2007), *Drug discovery and development: Understanding the R&D process* Washington DC. Pharmaceutical Research and Manufacturers of America. http://www.innovation.org/drug_discovery/objects/pdf/RD_Brochure.pdf

110 PhRMA (2012) New drug approvals in 2011. Washington DC Pharmaceutical Research and Manufacturers of America. http://www.innovation.org/sites/default/files/422/nda2011.pdf.

After the extensive research phase through which a potential drug candidate is identified, there is a long process of clinical trial activity, regulatory approval, and engineering and manufacturing phases before a new product is ready for marketing and distribution.

4.3 The research development process



Source: International Federation of Pharmaceutical Manufacturers and Associations (2012), The Pharmaceutical Industry and Global Health: Facts and Figures 2012, IFPMA. This diagram is designed to reflect the normal and historical process of development for the global pharmaceuticals market.

Comparisons with small molecule business models

The process of getting biopharmaceuticals to market is broadly similar to traditional pharmaceuticals, although it is often slightly more costly and time intensive. The business model for biopharmaceuticals is also a little different.

Before biotechnology, drug innovation relied on large scale, relatively automated processes. In the absence of a detailed understanding of the underlying reasons for most diseases, large-scale screening processes were undertaken to match a large number of drug candidates against a relatively small number of known disease targets.[111] Biopharmaceutical drugs such as antibody therapeutics generally have a specific clinical target and the mechanism behind the target drug interaction is better understood.

In general, biopharmaceuticals are traditionally delivered by injection in a clinical setting and, being better defined (or more specific) to the clinical target population, have a smaller potential market. Indeed many of the biopharmaceuticals developed to date must be administered in a hospital or clinic setting, which creates a niche market rather than the broader general practice/primary care market.[112]

111 Rasmussen 2007, Response of Pharmaceutical Companies to Biotechnology: Structure and Business Models, Working Paper no. 33, Centre for Strategic Economic Studies, Melbourne.

112 Ibid, p. 9.

This, combined with risk and cost issues explored further below, feeds through to differences in revenue models, as the 'blockbuster' model that typifies pharmaceuticals is arguably less significant with respect to biopharmaceuticals. Of total sales of $249 billion for the top 10 pharmaceutical companies in 2005, only $5.4 billion are biopharmaceuticals products (discussed later in this chapter).[113]

This better enables large pharmaceutical companies to pay for the cost of new R&D with existing product revenue dollars, whereas this is not the case for biotechnology companies.

While there are some biotechnology companies that are now large commercial corporations such as Genentech (now part of Roche), Amgen, Genzyme (now part of Sanofi), Gilead Sciences, and Vertex Pharmaceuticals, the majority of biotechnology companies are still not profitable. Based on 2009 net income, only 17 of 225 (7.5 per cent) public biotechnology companies in the drug development business were profitable, and those companies tended to have three or more products on the market.[114]

Positive net income in biotechnology is rare, even a couple of years after product approval. Executives of small biotechnology companies often hope to bring a product through the early phases of development and then have the product acquired or partnered by a larger company, or have the company bought out entirely. These licensing deals can be sufficient to recoup the full cost of R&D and make a profit.

Unable to fund R&D through revenue, biotechnology companies rely on other financing mechanisms to pay for innovation. These include venture capital funding, licensing deals with large pharmaceutical companies or larger biotechnology companies, public offerings, debt financings, private investments in public entities, and government funding.[115]

The commercial costs and risks of innovating and developing therapeutic biopharmaceuticals

Once an innovation is proved successful in a laboratory setting, there is an extensive and expensive process involved in converting research into biopharmaceuticals that are available to consumers.

Just like pharmaceuticals, the R&D process surrounding the innovation and development of therapeutic biopharmaceuticals (including recombinant proteins and monoclonal antibodies) is characterised by high research and development costs, long product development timeframes and high failure rates.

The risks involved are considerable, the time lag between research and profitability is extensive, and large amounts of capital are expended with little or no return along the way. While there are success stories, there is no guarantee of success before you go into clinical trials, and 'failures' and 'sunk' costs characterise the sector.

There is mixed evidence on the difference in costs and development periods between biopharmaceuticals and traditional pharmaceuticals, although by and large it is

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113 Rasmussen 2007, Response of Pharmaceutical Companies to Biotechnology: Structure and Business Models, Working Paper No. 33, Pharmaceutical Industry Project, August.

114 Thomas, D. (Dec 16 2010). 'How Pro-table is the Biotech Drug Development Sector?' BIOtech NOW Blog of the Biotechnology Industry Organization (BIO).

115 BIO Ventures for Global Health (2012), Biotechnology: Bringing Innovation to Neglected Diseases Research and Development, California, United States, p. 19.

understood that biologics take a little longer, and are more costly to develop than traditional small molecule therapeutics.[116]

Chart 4.4 highlights the trajectory of research and commercialisation for biopharmaceuticals. It shows, as discussed further below, that it takes time and money to get research innovations to market, with considerable sunk costs, no guarantees of success, and inherent risk at each stage.

High research and development costs and substantial sunk costs

With up to 12–15 years of time and billions of dollars to be invested, medical research is said to have a longer and more costly path to develop new technologies to a marketable standard than other areas of technology research.[117]

Most studies on the costs of innovation and commercialisation of pharmaceuticals show a range in costs per approved drug of between US$1.4 billion and US$1.9 billion in 2011 dollars, including time costs and the cost of research into unsuccessful projects.[118]

These estimates have risen substantially over the years, with the earliest study estimating costs of $US199 million in 1969 (in 2011 dollars) (table 4.5).

Drivers of cost growth include higher cash outlays, ongoing increases in the average cost of capital for all companies, more expensive development phases in terms of out-of-pocket costs, declining success rates for clinical testing as more difficult therapeutic areas are targeted, and increased time requirements as laboratory and clinical testing procedures become more extensive and more complex.[119]

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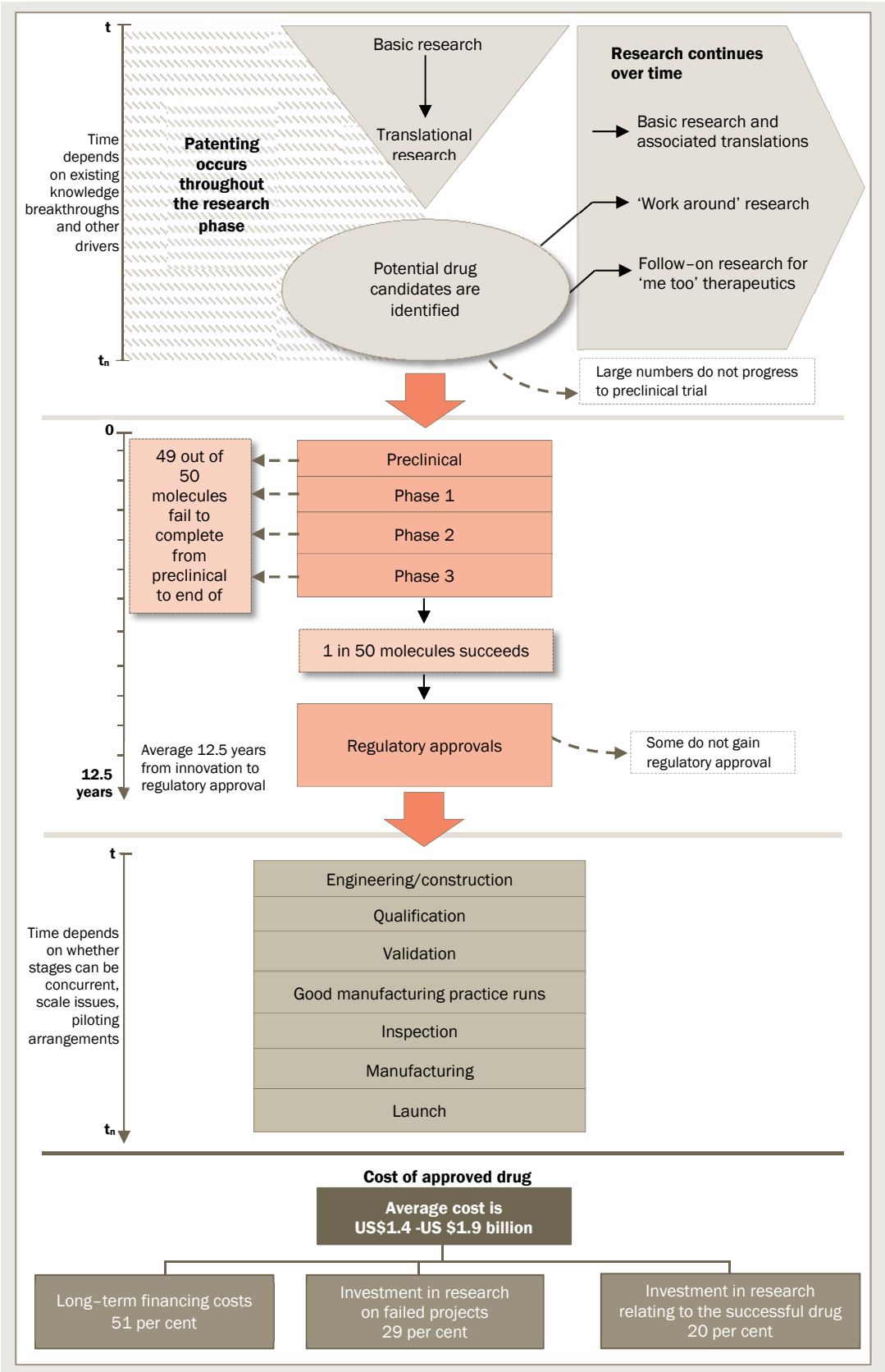
116 Jungbauer, A., U., Göbel BTJ Forum (2012), Biopharmaceutical process development — shortcut to market: an interview with Rolf Werner from Boehringer Ingelheim, *Biotechnology Journal*, 2012 Volume 7, 14–16

117 Medicines Australia (2013) Submission to Australian Government Pharmaceutical Patents Review.

118 Paul et. Al. (2010) How to improve R&D productivity: The pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery,* 9(3), 203–214.

119 Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom, p. 4.

4.4 The cost and development period for biopharmaceuticals



Data source: Created by the CIE. Cost estimates sourced from Paul et. Al. (2010) How to improve R&D productivity: The pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery,* 9(3), 203–214

4.5 Estimates of the full cost of bringing a new molecular entity to market

Source	US$m, 2011 prices	Published by:
Hansen, 1979	199	In Chien, R.A. ed. Issues in pharmaceutical economics. Lexington, MA: D.C. Heath and Company
Wiggins, 1987	226	Pharmaceutical Research and Manufacturers of America
DiMasi et al, 1991	451	N/A
Office of Technology Assessment, US Congress (OTA), 1993	625	US Government Printing Office
Myers and Howe, 1997	664	POPI working paper 41-97. Cambridge, MA: MIT Sloan School of Management.
DiMasi et al., 2003	1 031	Journal of Health Economics
Gilbert, Henske, and Singh, 2003	(1995–2000) 1 414 (2000–2002) 2 185	In Vivo
DiMasi and Grabowski, 2007	1 405 (biopharmaceutical) 1 493 (new molecule)	Managerial and Decision Economics, Vol 28, Issue 4-5
Adams and Branter, 2006	1 116	Health Affairs, 25(2)
Adams and Branter, 2010	1 560	Health Economics. 19(2)
Paul et al, 2010	1, 867	Nature Reviews Drug Discovery. 9(3)
Mastre-Ferrandiz et al, 2012	1 506	Office of Health Economics, London

Note: Caution should be taken in comparing across studies, which differ in many respects including in their use of their aggregate versus project-level data, variations in data in terms of drug vintage (the time period when drugs in the sample were first tested in humans or approved, and differences in sample sources (confidential surveys or publicly available information.) All values are adjusted to US$ 2011 prices using data for the US GDP implicit price deflators from the World Bank.

Some of these studies have been undertaken or funded by large pharmaceutical companies.

Source: Various, compiled in Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom.

Most of these studies combine pharmaceuticals and biopharmaceuticals in their cost estimates.

The only study focusing specifically on biopharmaceuticals estimated total costs of US$1405 million per approved new biopharmaceutical and US$1493 million per approved new (small) molecule (converted into 2011 dollars).[120] This draws on drug-specific data on cash outlays, development times, and success in obtaining regulatory marketing approval.[121]

Focusing only on R&D costs and excluding the cost of capital (time costs), costs per biopharmaceutical were US$633 million, of which $442 million or 70 per cent of the expenditure per successful drug is spent on failed projects and is of little ongoing value to the company (2011 dollars). Hence, approximately 70 per cent of the cost of developing each successful biopharmaceutical is a 'sunk' unrecoverable cost.

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120 Values are adjusted to US$ 2011 prices using data for the US GDP implicit price deflators from the World Bank to enable comparison with other studies. Estimates actually reported for 2005 were US$1 241 million per approved new biopharmaceutical and US$1 318 million per approved new molecule.

121 DiMasi, J. Grabowski, H. 2007, *The Cost of Biopharmaceutical R&D: Is Biotech different?* Managerial and Decision Economics, Vol. 28, Issue 4-5.

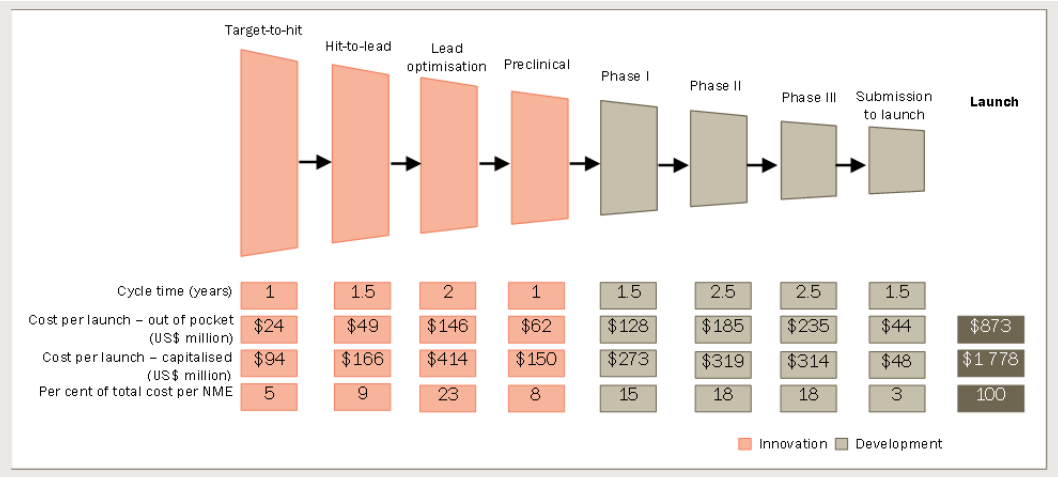
Most costs are incurred in the development phase

Paul et al (2010) breaks down costs across the R&D cycle. While this study is not specific to biopharmaceuticals, it is considered to be an appropriate guide to costs by R&D stage. This study found that the cost of developing a single new (small) molecular entity (NME) (capitalised) is US$1778 million (2008 dollars).[122]

While 46 per cent (US$824 million) of these costs are incurred in the innovation phase, the remainder 54 per cent (US$954 million) are incurred in the development phase.

Excluding the cost of capital, out of pocket expenses for development of a single NME were estimated at US$873 million, of which 32 per cent of costs relate to innovation and 68 per cent to development. Paul et al also suggests that the innovation of a single NME takes five and half years while the development phase extends a further eight years (chart 4.6).

4.6 R&D costs along the innovation — development continuum



Data source: Paul et al (2010).

The most expensive therapeutic area in terms of bringing drugs to market is anti-infective

Development costs can also vary depending on the therapeutic class of drug, with anti-infective drugs being the most expensive (table 4.7).

Of the 68 investigational compounds analysed for DiMasi et al (2010), four were recombinant proteins and two were monoclonal antibodies. One was a vaccine and the remaining 61 investigational compounds were small molecular compounds, which would only be related to a gene patent if the target (for example, receptor protein) has a gene patent on the isolated gene sequence and amino acid sequence. Hence, the proportion of the sample that is relevant to isolated human gene patents is small.

The broader observation that is relevant for this review is that there is variation in costs by therapeutic class.

122 Assumes a cost of capital of 11 per cent.

4.7 Research and development costs by therapeutic drug category

	Average	Cardiovascular	Central Nervous System	Anti-infective	Analgesic/ anaesthetic
	US$ million	US$ million	US$ million	US$ million	US$ million
Cost per approved drug[a]	282	277	273	362	252
Capitalised costs[b]	166	460	464	492	375

[a] Includes out-of-pocket clinical period costs per approved drug inclusive of failures. [b] Capitalised costs refer to out-of-pocket plus time costs.

Note figures are expressed in 2000 dollars.

Source: DiMasi, J. Grabowski, H. Vernon, J. 2004, *R&D costs and returns by therapeutic category*, Drug Information Journal; Vol 38(3) pp. 211–223.

Long development timeframes

Translating successful research into new efficacious and cost effective treatments, medicines, and therapies takes time.

There are varied estimates on the length of the development period, although most studies point to lead times of around 10 to 12 years to get a new product to market.

Focusing specifically on the development time through phases 1, 2, and 3 trials, development times are estimated to range from 75 to 79 months (6.3 to 6.6 years) (table 4.8).

Only one study focuses specifically on development times for biopharmaceuticals, which was found to be slightly longer than those for traditional pharmaceuticals. DiMasi and Grabowski (2007) found that the timeframe from clinical development to approval for biopharmaceuticals was 97.7 months (8.1 years), compared to 90.3 months (7.5 years) for pharmaceuticals.[123]

Hence, total clinical and approval time for biopharmaceuticals was 8 per cent longer than for pharmaceuticals. Nearly all the difference was found to be in phase I.

Previous work by Kaitin has estimated clinical and regulatory approval phase lengths by therapeutic class as shown in chart 4.9. This study suggests that clinical development times range from a relatively short period of 5.2 years for AIDS antiviral agents to periods of 7.9 years for antineoplastic agents. In the case of neuropharmacologic and cancer drugs, where the average time to obtain regulatory approval is added (1.7 and 0.8 years, respectively), the total time to bring a candidate drug from the start of human testing to market is nearly nine years (this excludes the preclinical, animal testing phase, as well as innovation and research).

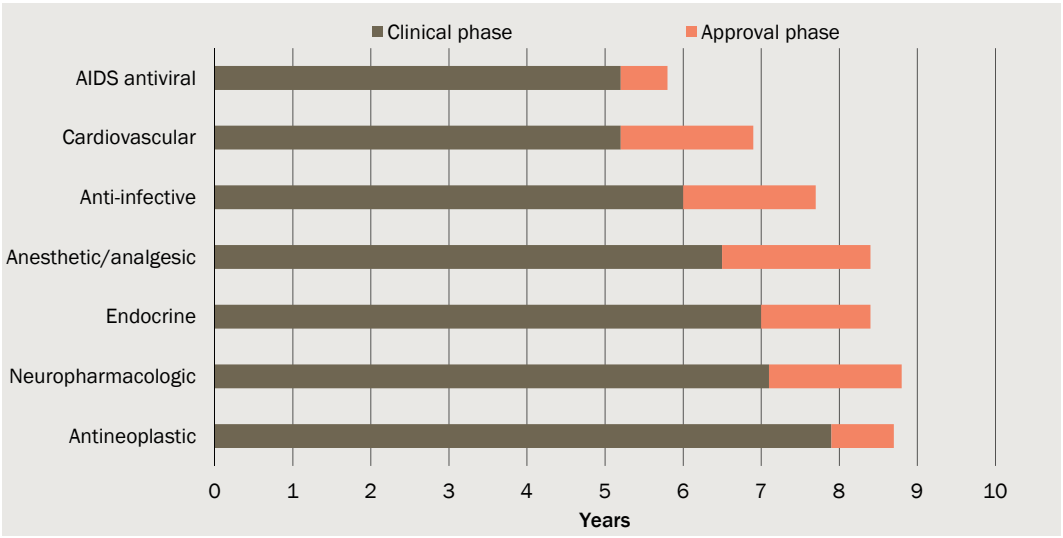
123 DiMasi, J. Grabowski, H. 2007, *The Cost of Biopharmaceutical R&D: Is Biotech different?* Managerial and Decision Economics, Vol. 28, Issue 4-5.

4.8 Development times

Source	Phase 1	Phase 2	Phase 3	Cumulative probability (Phase 1 to 3)	Cohort year
DiMasi et al, 1991	16.2	22.5	29.9	68.6	First tested in humans 1970-1982
DiMasi et al 2003	21.6	25,7	30.5	77.8	First tested in humans 1983-1994
Abrantes-Metz, Adams and Mertz 2005	19.7	25.1	41.4	86.2	Entered one of the stages of human clinical trials for the first time between 1989–2002
Adams and Branter, 2006	19	30	30	79	Drugs entering human clinical trials for the first time between 1989–2002
Keyhami, Diener-West and Power 2006	N/A	N/A	N/A	61.2	Drugs approved in the US between 1992–2002
Adams and Branter, 2010	16.6	30.7	27.2	74.5	Drugs entering human clinical trials for the first time between 1989–2002
Paul et al, 2010	18	30	30	78	1997–2007
Kaitin and DiMasi, 2011	N/A	N/A	N/A	78	New product approvals in the US 2000–2009

Source: Various. Compiled in Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom.

4.9 Mean clinical development and approval phase times by therapeutic class (USA 2003–2007)



Note: Clinical development times (from IND filing to NDA submission) and regulatory approval times (from NDA submission to approval) for new molecular entities approved by the US Food and Drug Administration during the five-year period 2003–2007, grouped by therapeutic area. Analysis by the Tufts Center for the Study of Drug Development, based on data included in its approved products database. The anti-infectives category excludes AIDS antiviral agents. IND refers to investigational new drug application and NDA to a new drug application.

Data source: Kaitin, K. 2010, Deconstructing the Drug Development Process: The New Face of Innovation, Nature America, Inc, Vol 87(3), March, p. 357.

High costs of capital

Extended development times have a direct impact on the cost of capital as R&D costs are incurred over extended periods — many years before any revenue is earned to recover them.

The costs of capital typically used in the literature to estimate the total costs of bringing a drug to market varies, but has increased over time from an estimate of 8 per cent in 1979 to around 11 in recent years. The only study that examined just biopharmaceuticals, assumed a cost of capital of 11.5 per cent (table 4.11).

The cost of capital for biotechnology companies focuses heavily on innovation and early stage development and is typically understood to be higher than for traditional pharmaceuticals. This reflects many factors, including the concentration of investments in earlier stage R&D, investors' relative lack of experience in dealing with biotechnology companies, and perceptions of managerial capabilities of smaller, newer biotechnology companies compared to larger, longer established pharmaceutical companies.[124]

4.10 Cost of capital for funding R&D

Source	Real annual cost of capital	Notes
Hansen, 1979	8 per cent	For R&D expenditures in the 1960s and 1970s
Wiggins, 1987	8 per cent	Used Hansen 1979 figure
DiMasi et al, 1991	9 per cent	Based on a CAPM analysis for sample of firms from mid1970s to mid 1980s
OTA, 1993	10, rising to 14, then back to 10 per cent	Applies to firms in the early 1980s
DiMasi et al, 2003	11 per cent	Based on CAPM analysis for firms over 1985-2000
Adams and Branter, 2006	11 per cent	Used DiMasi et al 2003 figure
DiMasi and Grabowski, 2007	11.5 per cent	Biopharmaceutical firms only using CAPM in years 1994, 2000 and 2004
Vernon, Golec and DiMasi, 2009	14.4 per cent	Fama-French based estimate. CAPM comparison was 11.02 per cent
Paul et al, 2010	11 per cent	Used DiMasi et al 2003 figure

Source: Various. Compiled in Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom.

High failure rates of drug innovation and development

The commercialisation of biopharmaceuticals is characterised by low phase transition probabilities.

124 Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom, p. 28.

Conventional industry wisdom is that approximately 30 per cent of all biopharmaceutical drugs entering clinical testing will ever reach the market, with 1 per cent of new lead compounds for new targets ever leading to a return on R&D costs.[125]

This is supported by empirical research. DiMasi and Grabowski estimate phase transition probabilities using information from the Tufts CSDD biotechnology database to calculate a clinical approval success rate of 30.2 per cent (as opposed to 21.5 per cent for pharmaceuticals).[126]

The International Federation of Pharmaceutical Manufacturers and Associations suggests that for every 250 molecules entering preclinical trial, only five will make it through to human trials and only one will reach the market.[127] Thus on average for each approved drug, a pharmaceutical company expects to invest in 49 drug trials that will fail.

Alternatively Paul et al (2010) estimated that for every ten drugs entering preclinical trial, only one is approved and many more candidates are identified without entering preclinical trial. However, this could refer to annual candidates required to enter phase I in order to get one drug approved each year.

Paul et al also found that only 8 per cent of new molecular entities successfully make it from point of candidate selection (moving from preclinical into phase 1) to approval. Given suggestions that new biologic drugs have a higher probability of launch than small-molecule drugs, this study assumed a success rate of 7 per cent for small-molecule drugs and 11 per cent for biologics.[128]

At the *innovation* stage, it is estimated that the overall probability of success is 35 per cent, across the four stages of target-to-hit, hit-to-lead, lead optimisation, and pre-clinical.[129]

More studies review success rates throughout the development stage (table 4.11), which show variable cumulative probabilities of success, typically lower than the cumulative probabilities estimated for the innovation phase. The most recent estimates suggest that the probability of success is:

- Phase 1: 49 – 75 per cent;
- Phase 2: 30 – 48 per cent, and
- Phase 3: 50 – 71 per cent.

Based on the lowest estimate for each phase, and recognising cumulative probabilities, 13.6 projects would be needed in phase 1 to achieve one approved new molecular entity.

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125 Jungbauer, A., U., Göbel BTJ Forum (2012), Biopharmaceutical process development — shortcut to market: an interview with Rolf Werner from Boehringer Ingelheim, *Biotechnology Journal*, 2012 Volume 7, 14-16.

126 DiMasi, J. Grabowski, H. 2007, *The Cost of Biopharmaceutical R&D: Is Biotech different?* Managerial and Decision Economics, Vol. 28, Issue 4-5, p. 472.

127 International Federation of Pharmaceutical Manufacturers and Associations (2012), The Pharmaceutical Industry and Global Health: Facts and Figures 2012, IFPMA.

128 Paul et at (2010).

129 Paul et at (2010).

The most optimistic estimates indicate that 3.9 projects would be required in phase 1 to achieve one approved new molecular entity.[130]

4.11 Probability of success by development stage

Source	Phase 1	Phase 2	Phase 3	Cumulative probability (Phases 1 to 3)	Cohort year
DiMasi et al, 1991	75	44.2	63.5	21.1	First tested in humans 1970–1982
Gilbert, Henske and Singh, 2003 1995-2000)	75	50	67	25.1	First tested in humans 1995–2002
Gilbert, Henske and Singh, 2003 2000-2002)	69	56	40	15.5	First tested in humans 2000–2002
DiMasi et al 2003	71	44.2	68.5	21.5	First tested in humans 1983–1994
Kola and Landis, 2004	60	38	55	12.5	First-in-man to registration drugs during 1991–2000
Abrantes-Metz, Adams and Mertz 2005	81	58	57	26.8	Entered one of the stages of human clinical trials for the first time between 1989–2002
Adams and Branter, 2006	100	74	46	34.0	Drugs entering human clinical trials for the first time between 1989–2002
Paul et al, 2010	54	34	70	12.9	1997-2007
Adams and Branter, 2010	75	48	71	35.6	Drugs entering human clinical trials for the first time between 1989–2002
DiMasi et al 2010 (1993-2004)	65	40	64	16.6	First entered clinical testing between 1993 and 2004
DiMasi et al 2010 (1993-1998)	67	41	63	17.3	First entered clinical testing between 1993 and 1998
DiMasi et al 2010 (1999-2004)	64	39	66	16.5	First entered clinical testing between 1999 and 2004
Pammolli, Magazzini and Riccaboni, 2011	68-49	58-30	80-50	31.6-7.4	Projects started between 1990 and 2004

Source: Various. Compiled in Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom.

130 Mestre-Ferrandiz, J, Sussex, J., and Towse, A. (2012) The R&D Cost of a New Medicine, Office of Health Economics. London, United Kingdom, p. 22.

Success rates by therapeutic class

Previous statistical analysis by DiMasi et al utilizes both public and private data sources to estimate clinical phase transition and clinical approval probabilities for drugs in the development pipelines of the 50 largest pharmaceutical firms.131 The clinical approval success rate in the US was 16 per cent for self-originated drugs (originating from the pharmaceutical company itself) during 1999–2004, while for all compounds; the clinical approval success rate for the study period was 19 per cent.

However, the estimated clinical approval success rates and phase transition probabilities differ significantly by therapeutic class. The estimated clinical approval success rate for self-originated compounds was 32 per cent for large molecules and 13 per cent for small molecules. The estimated transition probabilities were also higher for all clinical phases with respect to large molecules.

Table 4.12 shows the estimated clinical approval success rates for self-originated drugs, which varies substantially by therapeutic class. The CNS (8 per cent), cardiovascular (9 per cent), gastrointestinal/metabolism (9 per cent), and respiratory (10 per cent) categories had relatively low estimated approval success rates. In contrast, systemic anti-infectives had a relatively high clinical approval success rate (24 per cent).

4.12 Phase transition and clinical approval probabilities by therapeutic class for self-originated compounds first tested in humans from 1993 to 2004

	Phase I-II	Phase II-III	Phase III-RR	RR-approval	Clinical approval success rate
Antineoplastic/immunologic	71.8	49	55.3	100	19.4
Cardiovascular	62.9	32.4	64.3	66.7	8.7
CNS	59.6	33	46.4	90	8.2
GI/metabolism	67.5	34.9	50	80	9.4
Musculoskeletal	72.4	35.2	80	100	20.4
Respiratory	72.5	20	85.7	80	9.9
Systemic	58.2	52.2	78.6	100	23.9

Source: DiMasi, J. Feldman, L. Seckler, A. and Wilson, A. 2010, Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs, Clinical Pharmacology and Therapeutics. 87(3), 272-277.

The risks and uncertainties are not as high for diagnostics, as once the isolated gene sequence for a particular disease related gene has been identified and isolated, the development of the test is not as onerous as it is for medicines. There are also different regulatory frameworks governing the approval and listing of diagnostics and pharmaceuticals. The TGA requires that both commercially available and in-house In Vitro Diagnostic (IVD) medical devices follow regulatory requirements according to the Therapeutic Goods (Medical Devices) Regulations 2002. Commercial IVDs are tested for clinical efficacy and are listed on the ARTG. In-house IVDs are not supplied outside the laboratory, must comply with NPAAC (National Pathology Accreditation Advisory

131 The study examined the development histories of these investigational compounds from the time point at which they first entered clinical testing (1993–2004) through June 2009. See DiMasi, J. Feldman, L. Seckler, A. and Wilson, A. 2010, *Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs*, Nature Publishing Group, Vol 87(3), March.

Council) standards as developed by NATA (National Association of Testing Authorities) and are monitored by the TGA.

Rewards for risk through exclusivity

Pharmaceuticals and biopharmaceuticals would usually enjoy a period of market exclusivity, in recognition of the costs and risks required to be incurred to convert inventions into downstream innovations.

Patents are one of the instruments used to achieve this, and guaranteeing a period of market exclusivity through the patent system is widely viewed as necessary to mitigate the extraordinary risks for companies in investing in pharmaceutical R&D.

Patents have been shown to be able to alleviate some of the hurdles in generating net financial returns, depending on the wider need and demand for the patented claims. For example, the patent over erythropoietin granted to Amgen is reported to have earned the company in excess of $1 billion to 2009.[132]

There are also other sources of market exclusivity that are separate to patents applicable to pharmaceuticals that are outside of the patent framework.

This includes the data exclusivity period following a medicines inclusion on the Australian Register of Therapeutic Goods, which is currently five years. The data exclusivity period means the specific information provided to the Therapeutic Goods Administration in support of the pharmaceuticals registration process cannot be relied upon by a third party for a period of five years. This provides a specific period of exclusivity for the original, which is not connected to the patent status of the product, nor does it provide any extended patent. In some instances, data exclusivity can protect a patented invention that is no longer in force.[133]

In principle, periods of market exclusivity could afford market power to companies in the pricing of medicines, enabling companies to convert exclusivity into high reimbursement prices with relatively inelastic prices.[134] Australia's pricing mechanism and reference system operated under the PBS is complex, and recent reforms have been implemented to minimise reimbursement prices, so in practice it is difficult to substantiate that price premiums are achieved. Either way, the potential 'first-mover advantages' are deeply embedded into the business model for multinational pharmaceutical and biotechnology companies, which rely on large revenue streams from a selected number of patented products to fund the rest of the business.

Analysis based on 2005 data shows that the global sales of just 68 drugs by the top 10 companies by global sales represents 58.5 per cent of their sales (table 4.13).

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132 Cook-Deegan, R. and Heaney, C. (2010) Patents in genomics and human genetics. Annual Review of Genomics and Human Genetics, vol 11: 383–425

133 Therapeutic Goods Act (Cth) 1989

134 Inelasticity defines a situation in which the supply and demand for a good are unaffected when the price of that good changes. For instance, demand for a life-saving drug may be perfectly inelastic where people are willing to pay any price to obtain it — where the price increases dramatically the quantity demanded would remain the same.

In overseas markets, beyond the exclusivity period, the price and market share of branded pharmaceutical drugs tend to remain high after the branded drugs come off patent and chemically identical, but much cheaper, generic substitutes appear,[135] due to reputation effects, slow information diffusion, or the habits (or capture) of the medical profession.[136] This is not the case in Australia, where the PBS reimbursed price for originator and generic drugs is identical. The PBS scheme, through policy reform, has introduced price disclosure to enable generic firm discounts offered to pharmacies to be reflected in reduced listed prices for each molecule on the PBS.

While biopharmaceuticals currently comprise a small proportion of pharmaceutical sales, the pending expiration of patent protection of many of the largest selling blockbusters over the next several years is likely to see biopharmaceutical drugs become more important in future.

4.13 Blockbuster sales by major pharmaceutical companies, 2005

	Total pharma sales	Total blockbuster sales	Blockbuster ratio	Total blockbuster drugs	Biopharma sales	Biopharma blockbuster drugs
	$ billions	$ billions	No.	No.	$ billions	No.
Pfizer	44.28	28.28	63.9	8	0.05	
Glaxo	33.96	21.31	62.7	13	0.01	
Sanofi-Aventis	32.24	17.71	54.9	10	2.69	2
Novartis	24.96	9.28	37.2	5	0.05	
Astrazeneca	23.95	17.53	73.2	10	0.00	
J&J	22.32	15.34	68.7	7	0.05	
Merck	22.01	13.59	61.7	4	0.00	
Wyeth	15.32	7.74	50.5	4	0.05	
BMS	15.25	6.08	39.9	2	0.00	
Lilly	14.65	8.78	59.9	5	2.52	1
Total top 10	248.94	145.61	58.5	68	5.38	2

Note: Blockbuster' drugs include those with global sales exceeding $US1 billion

Data source: Rasmussen 2007, Response of Pharmaceutical Companies to Biotechnology: Structure and Business Models, Working Paper No. 33, Pharmaceutical Industry Project, August.

As discussed below, the period of exclusivity in the USA appears to have been in sharp decline since the 1970s. This shows that patents, while still important, are having less and less of an impact on ensuring that companies attain a period of monopoly status with respect to pharmaceuticals. This results from the ongoing extensions to the time required for development, as scientific testing procedures become more complex, and the increasing presence of follow-on companies in earlier stages of the R&D continuum, who are ready to go to market when exclusivity periods expire.

135 Posner, R. 2005, *Intellectual Property: The Law and Economics Approach,* Journal of Economic Perspectives, Vol 19 (2), pp. 57–73

136 Boldrin, M. and Levine, D. 2004, *The Economics of Ideas and Intellectual Property*, p. 7.

Impacts on follow-on (generic) innovation and development

'Follow-on' drugs refer to products that have a similar mechanism of action to pre-existing drugs. These drugs are important given that they inject price competition into the marketplace and often provide better therapeutic options at the individual patient or patient subgroup level.

Research by DiMasi and Paguette suggests follow-on innovation and development of drugs largely occurs simultaneously rather than subsequent to first-in-class drug approval.[137] That is, many follow-on drugs enter development long before the first drug in a new class is approved. Since the 1980s, every therapeutic class had at least one follow-on drug with initial pharmacological testing prior to the approval of the class breakthrough drug.

Australian data on the effective patent term (from TGA approval to patent expiry) suggests that the average effective patent term over the past several years had been 13–15 years.[138]

The trend towards greater concurrency in the development of drugs has increased. In 1995–98, all therapeutic classes had at least one generic drug that had made it to phase II testing before the first drug in the class was approved. Ninety per cent of therapeutical classes had at least one drug with phase III testing initiated before the first-in-class drug was approved (up from 25 per cent in 1980-84) (chart 4.15).

This increasing trend towards earlier and concurrent development means that such research is likely to be 'market-ready' once patent exclusivity on the first-in-class drug has expired.

Given that R&D by generic companies largely occurs concurrently, parallel development rather than imitation by generic drugs ensures that these products reach the market as soon as patent exclusivity expires.

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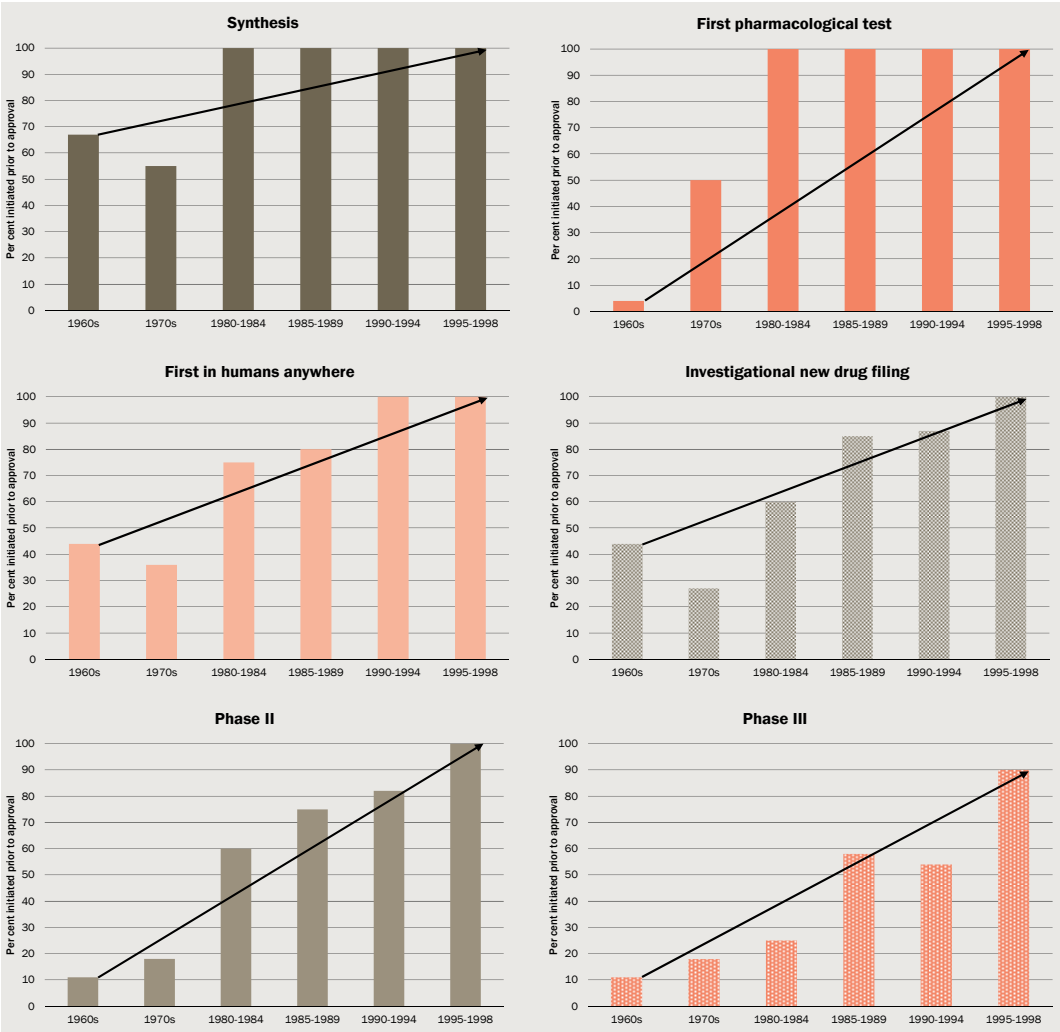
137 DiMasi, J. Paquette, C. 2004, found that the period of marketing exclusivity that a breakthrough drug enjoys has fallen by around 88 per cent from a median of 10.2 years in the 1970s to 1.2 years for the late 1990s in 'The Economics of Follow-on Drug Research and Development — Trends in Entry Rates and the Timing of Development', Pharmacoeconomics, Vol 22(2) pp. 1–14.

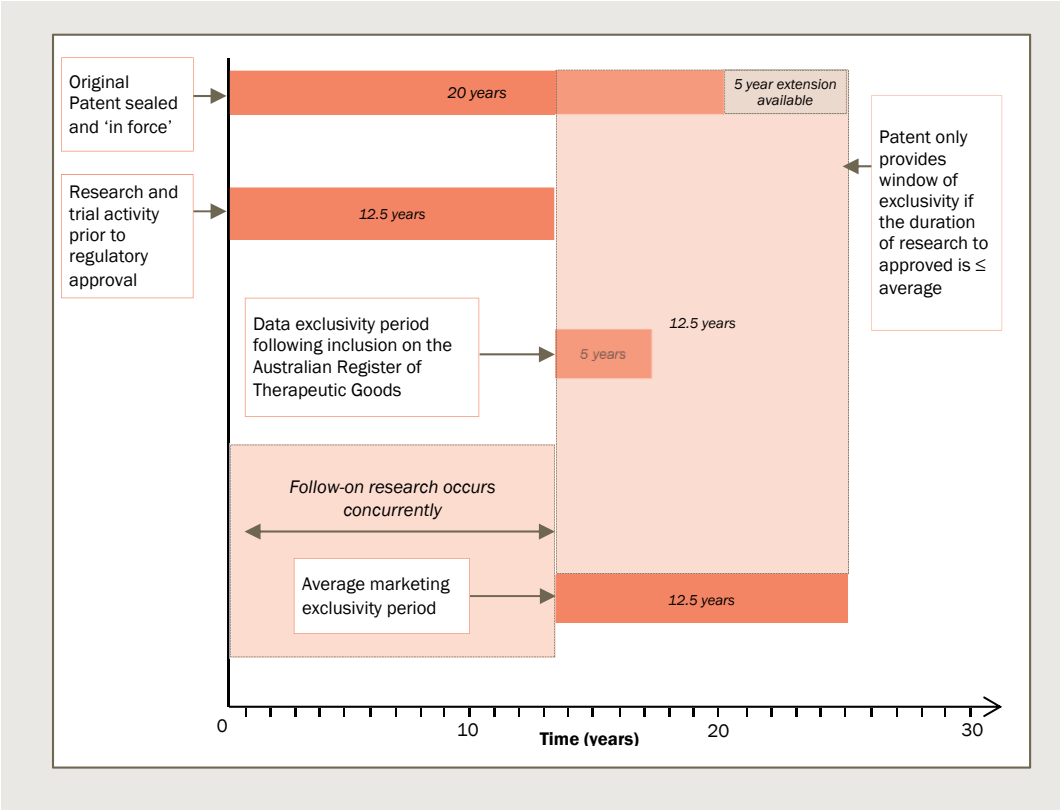
138 IP Australia, unpublished.

4.14 Research phase undertaken by generic companies before first-in-class approval



Data source: DiMasi, J. Paquette, C. 2004, The Economics of Follow-on Drug Research and Development - Trends in Entry Rates and the Timing of Development, Pharmacoeconomics, Vol 22(2) p. 9.

4.15 Stylised example of the effective patent term related to isolated human gene patents



Source: The CIE.

Where IP fits in: maximising the translation of research into products

Intellectual property rights is a key driver of the commercial return on medical research and the bringing of new medicines and treatments to market, as well as the enhancement of their efficacy and cost effectiveness. In most cases, IP protection has a critical impact on the incentives to invest in translational medical research.

Research also shows that patents improve the likelihood of successful research commercialisation. Research by the Intellectual Property Research Institute of Australia (IPRA) based on a sample of 3736 Australian inventions that were *potentially* patentable, found that possession of a patent raises the probability that the invention will be commercialised by between 2.0 and 8.0 percentage points (table 4.16),with the lower bound applying to commercialisation for export, which are more susceptible to patents being granted in export markets.[139]

That said, patent protection is a necessary, but not sufficient condition for investment in R&D (being among one of many drivers to invest).

139 Webster, E. Jensen, P. 2009, *Do Patents Matter for Commercialization?* Intellectual Property Research Institute of Australia, Working Paper No. 03/09, March.

4.16 Marginal effects on the probability of attempting each stage of commercialisation, patent applications 1989–2005

	License or spin-off	Development	Make and sell	Mass production	Export
	%	%	%	%	%
Existence of patent grant	3.6	2.5	5.9	8.0	2.0

Source: Webster, E. Jensen, P. 2009, *Do Patents Matter for Commercialization?* Intellectual Property Research Institute of Australia, Working Paper No. 03/09, March.

Other incentives for generating and sharing new knowledge

Patents are not always part of the product-to-market story for medical research. As highlighted previously in chapter 2, there is a large and growing volume of human genetic research being undertaken by universities, MRIs, CRCs, and public hospitals that has an 'incidental' interaction with the patent system, if at all.

There are also examples around the world of research-based pharmaceutical companies producing some medicines free of charge and/or donating unlimited supplies of drugs, particularly for neglected tropical diseases (NTDs) in developing countries.

For instance, in January 2013, 13 pharmaceutical companies, the governments of the US, the UK and the United Arab Emirates, the Bill and Melinda Gates Foundation, the World Bank, and other global health organisations launched a new collaboration to accelerate progress towards eliminating or controlling 10 NTDs by the end of the decade. This includes the expansion of drug donation programs (with pledges to donate 14 billion treatments over the 10 years from 2011 and 2020) and sharing expertise and compounds to accelerate R&D for new drugs, among other things.[140]

There is also translational research being funded by philanthropic organisations such as the Bill and Melinda Gates Foundation to ensure that critical products are delivered to populations that are unable to pay market prices for access to medicines, treatments and vaccines.

The Bill and Melinda Gates Foundation have developed Global Health Data Access Principles in order to make data widely and rapidly available to the broader global health community and generate the fullest possible public health benefits from data. These principles apply to data generated from activities sponsored in whole or in part by the Bill and Melinda Gates Foundation. Grantees are required, as a condition of a grant award, to facilitate the prompt and broad dissemination of data in accordance with these principles. For grants over $500 000, this will begin with development and submission of a plan that addresses how data access will be ensured, including a timeframe for data release.[141]

140 IFPMA 2012, Ending neglected tropical diseases, Geneva: International Federation of Pharmaceutical Manufacturers and Associations. http://www.ifpma.org/fileadmin/content/Publication/2012/IFPMA-NTD-NewLogoJUNE2.pdf

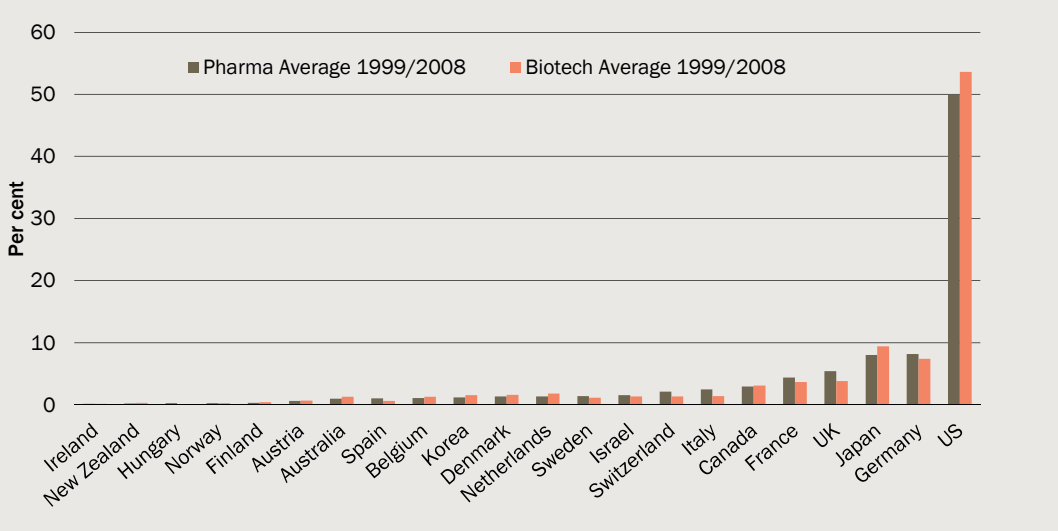
141 Bill and Melinda Gates Foundation 2011, Global Health Data Access Principles, April.

Australia is a small player in the global pharmaceutical and biotech market

Inventors in Australia hold a small proportion of world patents, representing just 1.3 per cent of total pharmaceutical and biotechnology patents at the USPTO and European Patent Office (EPO). International patent activity is heavily concentrated in OECD countries (chart 4.17). In the pharmaceuticals sector, inventors with the US as their country of residence accounted for around 40 per cent of total patents granted, while Germany, Japan and the United Kingdom accounted for 8.8 per cent, 7.8 per cent and 5 per cent respectively.

In the biotechnology sector, inventors with the US as their country of residence accounted for around 43.5 per cent of total patents granted, while Japan, Germany and the UK accounted for 8.9 per cent, 8.9 per cent and 3.9 per cent respectively.

4.17 Average share of pharmaceutical and biotech patents by country



Data source: OECD patent database and the CIE.

Table 4.18 illustrates the total number of patents granted by the USPTO and EPO both globally and to Australia in the biotechnology and pharmaceuticals industries over the decade to 2008.

4.18 Biotechnology and pharmaceutical patents issued by USPTO and EPO

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	307	326	300	308	277	300	265	254	263	280
World	28 816	29 011	28 591	28 411	27 648	26 264	25 282	23 546	22 178	22 613
Australian share (%)	1.07	1.12	1.05	1.08	1.00	1.14	1.05	1.08	1.19	1.24

Note: Figures are aggregated from OECD patent by technology database — patent grants at the USPTO plus patent grants at the EPO — for both pharmaceuticals and biotechnology technology domains (reference country equal to 'Inventor(s)'s country(ies) of residence' and reference date equal to 'Priority date').

Source: OECD patent database and the CIE.

When considering applications filed under the Patent Cooperation Treaty (PCT), the Australian share of total patent applications is slightly higher (average of 1.6 per cent over 1999 to 2008). Furthermore, while world PCT applications for biotechnology and pharmaceuticals have grown by only 0.8 per cent over the decade to 2008, PCT

applications made by Australians have grown by 7.8 per cent over the same period. Australia's share of global patent applications filed under the PCT is therefore increasing (table 4.19).

4.19 Biotechnology and pharmaceutical patent applications filed under the PCT

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
Australia	296	321	361	335	346	310	342	326	345	319
World	19 862	22 332	21 865	21 245	20 696	20 314	20 231	20 313	20 862	20 020
Australian share (%)	1.49	1.44	1.65	1.58	1.67	1.53	1.69	1.60	1.65	1.60

Source: OECD patent database and the CIE.

Despites its relatively low base, data collected by the Australian Department of Industry, Innovation, Science, Research and Tertiary Education (DIISRTE) shows that biotechnology was the fastest growing Australian technology group over 2005–2009 measured by growth in patents granted. Despite a decline in 2008, the number of patents granted to Australians in Australia rose into the double digits from 2006 onwards (table 4.20).

4.20 Biotechnology patents granted to Australians in Australia

	2005	2006	2007	2008	2009
	No.	No.	No.	No.	No.
Biotechnology	8	16	43	60	38

Source: DIISRTE Intellectual Property Scorecard 2005-2009, available at:
http://www.innovation.gov.au/Innovation/ReportsandStudies/Pages/IPScorecard2005-2009.aspx

While the stocktake of isolated human gene patents provided in Chapter 3 indicates isolated human gene patent applications are falling and changing over time, the broader signal from the biotechnology patent data is that Australia has developed a core research capacity in biotechnology. The DIISRTE[142] utilises the Revealed Technological Advantage (RTA) index from United States Patent and Trademark Office (USPTO) data to show that Australians have a comparative advantage in patenting biotechnology in the US relative to the rest of the world, and has had for some years.

Australia's commitments under TRIPs and other international agreements

The World Trade Organisation (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) establishes, inter alia, the minimum standard for intellectual property rights protection in the national systems of each World Trade Organisation member state — and therefore Australia.[143]

The Agreement requires member states to make patent protection available for any inventions, whether products or processes, in all fields of technology without discrimination. In its submission to the Senate Inquiry, IP Australia noted that it

142 Now DIICCSRTE, Department of Industry, Innovation, Climate Change, Science, Research and Tertiary Education.

143 Australia became a member of the WTO on 1 January 1995.

therefore 'assesses applications for gene patents by applying the same patentability requirements as for all other applications, irrespective of their technological field.'

However, the ALRC's 2004 report noted that, although TRIPS places constraints on the degree to which gene patents may be singled out for special treatment, 'the extent of these constraints is not clear'.

The Agreement also provides the right for member states to provide limited exceptions to patent rights that could be applicable to gene patents including:

- an exclusion to protect public order (*ordre public*) or morality as a result of commercial exploitation in a member's territory (replicated in AUSFTA); and
- an exclusion from patentability for methods of diagnostic, therapeutic and surgical treatment of humans (replicated in AUSFTA).

Australia is also a member of the APEC Intellectual Property Expert's Group (IPEG), which promotes TRIPS-consistent intellectual property protection among APEC trading partners and is a signatory to the Australia-United States Free Trade Agreement, which replicates the TRIPS requirements for non-discrimination and grounds.

There is no firm consensus among stakeholders and no legislative case law that determines the extent to which the terms and exclusions of TRIPS and related agreements dictate the international legal patentability of isolated human genes. However, Australia is obliged to honour its commitment under these international intellectual property agreements, including through application to international isolated human gene patentability.

5 *Valuing the benefits and costs of isolated human gene patents*

Isolated human gene patents should help facilitate the commercialisation of human genetic technology inventions, patents generate income for researchers and play a key role in spurring and incentivising innovation across the biomedical research sector. While it is expected that most patents underpinning new products involve patents over recombinant DNA technologies, some would also be isolated human gene sequent patents.

The estimated annual return of royalty and associated income to Australian entities of the subset of patents relating specifically to isolated human gene sequence patents currently held is in the order of $1.1 million to $2.6 million.

In some cases, price premiums are available to patent holders for sales of end-products underpinned by a patented upstream human genetic technology. Price premiums for innovative therapeutics with a large market are likely to be around 10 per cent on average, although this is not necessarily (and may indeed not be) attributable to the patent. Data on price premiums for patented diagnostic tests is similarly opaque, although some price premiums are apparent.

However, isolated human gene patents can be problematic and in some cases, costly. There are invariably trade-offs, which at times could be considerable and undermine benefits. The major trade-offs include actual or potential blockages and restrictions to research, compliance and enforcement costs that exist whether or not the patent has any market value, and costs associated with the lack of competition which is embedded in the IPR regime.

The challenges of attribution: how much do patents matter?

Patents currently underpin much of the human genetic related R&D to help better diagnose or treat health conditions based on a patients' genes, particularly that involving private R&D.

However, there are regulatory, market-based, scientific, and other factors that influence how much human gene-related R&D is funded, how research translates into improved health outcomes, and what the impacts are of newly available genetic technologies.

As observed previously, isolated human gene patents are not the only incentive to innovate or invest, but in some cases, and almost always with respect to translational research, they can be vital and fundamental to attracting large-scale investment for high risk research. Many stakeholders consulted in this review highlighted that for biopharmaceuticals, patents (which could include isolated human gene sequence patents) are considered to be a necessary but not sufficient condition to invest in bringing new therapeutics and vaccines to market.

'Which patent is the one that matters?' is also a challenging question. In some cases, it will be the upstream patent that genuinely matters to the research journey that ultimately produces advancements in medical research. In other cases, there will be a large number of patents that matter, not including any claims over isolated human gene sequences.

A notable feature of biomedical research is that complex research paths are required to fully exploit the potential of upstream inventions like isolated human gene patents. Much basic research forms the foundation for later research and there are many steps between initial pioneering research and what consumers would consider to be end-products. Patents are granted at every stage of the development pipeline, and researchers developing downstream products require access to patents at the upstream end of the drug development continuum to conduct later stage research and commercialise products.[144]

Value compared to what?

Irrespective of the extent to which patents are important to incentivising innovation, the *value* of patents is very much a relative concept — it depends on the benefits and costs that are avoided or foregone, which might otherwise have been available under alternative arrangements to the existing patent system. This 'alternative state' cannot be readily observed, with the vast bulk of human gene related research being undertaken internationally, where the patent system is deeply entrenched in R&D business models relating to biomedical research.

Exemptions exist, but they are rare and specific. By and large, therapies built on patented sequences that remain in-force, or therapies developed under free information sharing agreements, are only provided as part of the corporate social responsibility of global companies in cooperation with international agencies to help manage disease in developing countries that do not have the capacity to pay market prices for medicines.

The nature of patenting is also changing, which can impact on what is patentable, and hence, what the alternative to patents actually is. As highlighted previously, the HGP and its successors, and the rapidly changing area of genetic science, impacts on what is patentable over time. Rather than constructing an 'alternative state' against which the existing economic footprint of patents can be compared, the following analysis addresses a series of propositions to illuminate the types of benefits and costs that are likely to be attributable to isolated human gene patents in different situations, keeping this 'notional' concept of relativity in mind.

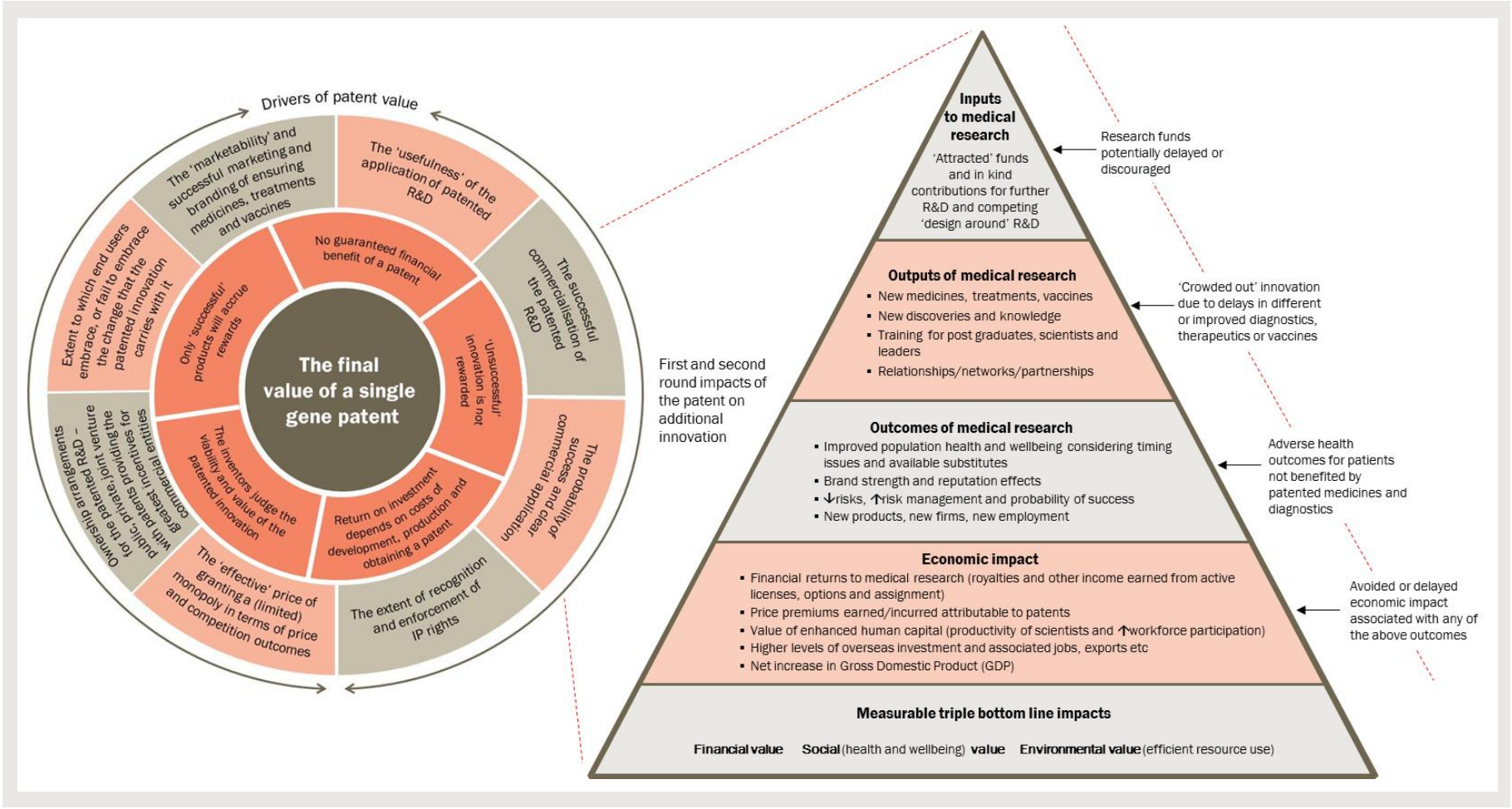
In doing so, this chapter provides guidance on the orders of magnitude of benefits and costs that likely to be attributable to the patenting of isolated human genes by considering the causal pathways (and uncertainties within them) that result from the granting and use of isolated human gene patents.

Understanding benefits and costs

The key drivers of patent value, and types of (positive and negative) impacts associated with isolated human gene patents, are summarised in chart 5.1 and explored further below.

144 Nicol and Nielsen 2003, op. cit., p. 15.

5.1 Factors that affect the economic value of isolated human gene patents



Data source: The CIE.

In many cases, whether these impacts are 'positive' or 'negative' can depend on how patents transpire and how patent holders and other entities behave and respond. For instance:

- the attraction of essential private sector funding for R&D related to human genes might simultaneously delay or restrict R&D investment from others;
- major medical breakthroughs in treatment might be partially discounted if the associated restrictions to competition in provision prevent or delay refinements and improvements in product quality and efficacy; and
- the need to support the intellectual property framework through enforcement, and to pay for it through patent application and renewal fees may introduce inefficient costs when the patent itself is not delivering 'value', with high failure rates and the commercial challenges of bringing new medicines to market highlighting the opportunity costs of patented isolated human genetic technologies.

Ultimately, the value of a patent is judged on its ability to encourage the availability of new and useful technologies to society, and to encourage innovation through encouraging the diffusion of knowledge, *beyond that which would be the case in their absence.*

There will always be a trade-off within the system because patents (nor any other instrument) can never make a 'perfect market'. This is because the field of biomedical research is distorted by purposeful interventions right across the research continuum as society tries to strike a balance between providing access to high quality health care, and achieve an efficient sharing of the costs of delivering health outcomes — across those that are sick and well, young and old, and in today's and in future generations.

Trade-offs are inevitable and this report seeks to help assess if and where trade-offs may exist, and when isolated human gene patents are at their most valuable.

The 'worth' of isolated human gene patents

The starting proposition of patent valuation is that the value of a patent depends in large part on how the patent holder intends to exploit its patent right, making 'value' a relative, and variable, concept.

Essentially patents are commercial assets, capable of generating positive economic benefits directly and/or indirectly.

Direct economic benefits include additional cash flow that may be created by patent rights.

Indirect economic benefits include those that may be derived from:

- money saved for the rights holder by reducing production and input costs;
- the signal that patents provide regarding R&D strength that helps the patent holder to raise investment capital and build other investment lines;
- market advantages obtained defensively to prevent competitors from obtaining similar patents and to raise the costs for competitors to enter a given market;

- bargaining strength if a patent forms part of a patent portfolio to improve a firm's bargaining leverage in both cross-licensing deals and patent infringement suits; and
- ultimately improved health outcomes as a result of access to pharmaceuticals and clinical practice that delivers net social (improved health and wellbeing) and economic (improved productivity and workforce participation) benefits.

There are several theoretical paradigms that are used in patent valuation to put a price on a patent (see box 5.2). None are perfect, and the following analysis takes the intent of each to draw together the evidence on benefits and costs to help assess the value of patenting isolated human genetic technologies.

Income earned

Income derived from a patent is one measure of aggregate net economic benefits from the asset being valued. In the case of patents relating to human genetic technologies, it is virtually impossible to anticipate all the possible future occurrences and usages that will affect the future income that a patent right will generate.

- For early-stage technologies, uncertainty surrounds almost all the critical aspects that will go into the patent rights' ability to generate an earnings stream.[145]
- For later stage translations of research, income from downstream products might be wholly attributable to the original isolated gene sequence patent or incidental to it. Either way, not all income generated by a new therapeutic can be attributed to the upstream isolated human gene patent that secured its entry into preclinical and later stage clinical trials.

This analysis considers two elements to provide an order of magnitude around the value of isolated human gene patents based on the income approach. These include:

- the value of royalties and licence fees returned to the patent holder; and
- price premiums achieved for products that are underpinned by a patent associated with the period of market exclusivity that is afforded by the patent.

Royalties and other income attributable to isolated human gene patents

The financial arrangements associated with the large majority of isolated human gene patents are strictly commercial in confidence, although are understood to vary substantially in terms of the structure of payment milestones and the dollar values involved.

Indeed the negotiation process that determines the financial flows between parties highlights that there can be marked differences of opinion between patent holders and potential licensees on what the patent is worth. This is due to the tendency of patent holders to value the patents' book value rather than market value, seeking to recoup the funds spent over time on research that resulted in the innovation. Potential licensees will

145 Murphy, W. Orcutt, J. Remus, P 2012, *Patent Valuation; Improving Decision Making through Analysis*, John Wiley & Sons, New Jersey.

take a different view, seeing a patent that has not yet been tested, and in the case of provisional patents, not even yet granted.

The licencing model adopted will also have an impact on the financial returns that accrue to a particular patent, with three broad models used (box 5.3).

5.2 Putting a price on a patent

With other commercial assets, the market is often referred to as the penultimate arbiter of value — the *market-derived price method* is the most accurate reflection of what an asset is worth. However, as highlighted throughout this report, the ingredients for a competitive patent market do not exist. For instance, the patent market is characterised by:

- **information deficiencies** — given that patents cover new technology with little to no commercial track record,[146] uncertainty about the future performance of patents is extreme meaning that the potential pool of buyers for patent rights is generally shallow. Asymmetric information between the patent holder and the potential acquirer of the patent rights creates a classic *lemons problem* where buyers are unable to distinguish the value of a patent and buyers tend to underpay for good patents and overpay for bad ones. These information problems, which stifle accurate market valuation of patents, stem from a lack of publicly disclosed patent transactions; and
- **comparability problems** — legislative requirements mean that patented inventions are necessarily 'novel' making it difficult to value patents based on similar transactions.

Given these constraints to the market valuation of patents, there are two other approaches to valuing patents (both of which have their limitations):

- the *income method*, which attempts to measure the aggregate net economic benefits (usually expressed in terms of free cash flow or net profits) that will come from the asset being valued — as income will be one of the economic benefits that drive a firm's asset decisions; and
- the *cost of development method*, which suggests that a patent should be worth at least the amount it cost to develop the patented technology and obtain (and maintain) the patent rights.[147] This would ordinarily be used to set a lower bound value, although in the context of isolated human gene patents with high failure rates, costs are rarely a useful construct for valuation. A better measure is to consider 'investment at risk', that is costs that would not be incurred because the incentive to invest would be insufficient, which is likely to be a better measure of a lower bound value.

146 With early stage technologies, there are seldom any meaningful historical results from which future results may be extrapolated.

147 Murphy, W. Orcutt, J. Remus, P 2012, *Patent Valuation; Improving Decision Making through Analysis*, John Wiley & Sons, New Jersey.

5.3 Licensing models associated with isolated human gene patents

The open access model — Cystic fibrosis (CF) is a commonly tested autosomal recessive disorder associated with mutations in the cystic fibrosis transmembrane conductance regulator gene. CF genetic sequences, mutations and methods for detecting them were patented by the Hospital for Sick Children, University of Michigan and Johns Hopkins University. Patents have been nonexclusively licensed for diagnostic use — licenses have been granted to over 60 providers of genetic testing — while patents have been variably licensed for gene transfer, commercial and other therapeutic applications.[148]

Exclusive use model — BRCA1 and BRCA2 are major genes in which mutations cause a strong breast/ovarian cancer susceptibility. Several patents on BRCA1 and BRCA2 were granted to Myriad by the USPTO and EPO. In the United States, Myriad initially required all diagnostic testing be done at its own US-based laboratory. However, unacceptably high costs for most service laboratories led to Myriad developing a licensing strategy that exclusively licensed the test to a limited number of commercial genetic laboratories within specific geographical regions.[149] In Australia, is the BRCA patents are still in force, however the licensee has not enforced its patent rights.

Another example is the patent held by Athena Neurosciences, which holds the patent on the apolipoprotein E (APOE) gene, associated with Alzheimer disease. The patentee does not allow other laboratories to screen for mutations in the APOE gene, meaning that laboratories are not able to test to determine whether a patient carries a genetic predisposition, even though testing can be conducted without using any product or device made by the patent holder.[150]

Controlled competition model — the third approach has been taken by Bio-Rad, the US based company that acquired the patent on the hereditary hemochromatosis (HFE) gene and its known mutations from other companies. Bio-Rad developed its own kits for two common HFE mutations and then marketed these kits as an alternative to licence fees. While licensing was an option available to laboratories performing testing, the cost involved made Bio-Rad's own commercial test kit more economically attractive. Licensing involved upfront payments and a per test fee of $20 for the two mutation responsible for the majority of cases.[151] The rigid licensing policy has resulted in many US laboratories refraining from developing their own kits for the disease. In Australia, Bio-Rad has been less assertive in enforcing its patent rights, possibly because the market is so much smaller and testing would be likely to decline sharply. Consequently, the impact of the HFE patent in Australia to date has been minimal.[152]

Source: Matthijs, G. and Hodgson, S.2008, *The impact of patenting on DNA diagnostic practice*, Clinical Medicine Vol 8(1), February.

148 National Institutes of Health 2010, *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Cystic Fibrosis: Patents and Licensing for Cystic Fibrosis Testing*, Genetics in medicine, Vol 12(4 Suppl), s194-s211.

The only public source of information on income flows associated with patents is available from the National Survey of Research Commercialisation, which provides data on the total value of income (including the value of running royalties and other forms of income) yielded from active licences, options and assignments (LOAs) for medical research institutes and universities across Australia.

Table 5.4 shows patent commercialisation data for all Australian publicly funded research organisations — including universities (most of which would be unrelated to medical science), medical research institutes and other publicly funded agencies.

In 2009, total income earned from active licences, options, assignments (LOAs) for MRIs across Australia was $22.2 million, and was $318.8 million for all research institutes (universities and MRIS), a proportion of which would relate to isolated human gene patents.

In the absence of data on the income flowing to holders of isolated human gene patents in particular, the direct financial returns to isolated human gene patent holders can best be derived from the average returns recorded as having accrued to patent holders.

Based on the National Survey of Research Commercialisation, the average income yielded per active LOA was $173 500 for total publicly funded research organisations and $71 500 for MRIs, although there is substantial variation across patents (chart 5.5). The limitations of 'average' LOAs are acknowledged, and highlighted in box 5.6.

5.4 Value of patents to Australian publicly funded research organisations, 2009

	Medical research institutes	Total publicly funded research organisations
Total patents or plant breeders rights (PBR) issued	77	867
Total number of LOAs active	310	1 838
Income yielded from active LOAs ($ millions)	22.16	318.84
Average income yielded from active LOAs (per LOA active)	71 495	173 470
Start-ups dependent upon licensing/assignment for initiation	24	216

Note: Australian publicly funded research organisations includes universities, publicly funded research agencies and a range of Medical research institutes. 'Active LOAs' refers to 'legally enforceable' licences and options that earned income in the reporting year, or which are contracted to provide income in future years and for which there is a reasonable expectation that income will be paid, or, when there is no financial consideration associated with the LOA, that the LOA reflects a continuing relationship between parties.

Data source: National Survey of Research Commercialisation 5th Iteration (2008-2009) and the CIE.

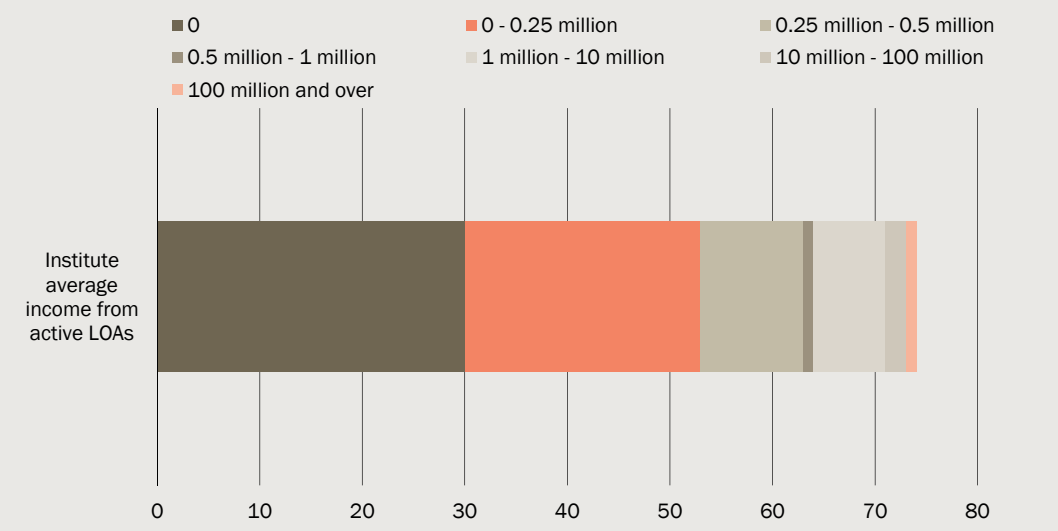
149 It is noted that types of mutations were only detected because different genetic laboratories were infringing the patents and continuing to test breast cancer patients for mutations. Furthermore, several manufacturers refrained from developing novel tests for BRCA1 and BRCA2 mutations because of these patents.

150 Andrews, L.2002, Genes and patent policy: rethinking intellectual property rights, Nature Publishing Group, Vol 3, October.

151 Merz, J. Kriss, A. Leonard, D. Cho, M. 2002*, Diagnostic testing fails the test,* Nature 415:577–9.

152 Royal College of Pathologists of Australasia 2010, Response to the Senate Community Affairs Committee Inquiry into Gene Patent.

5.5 Distribution of income across publicly funded Australian research institutes



Data source: National Survey of Research Commercialisation 5th iteration (2008-09).

For instance, across all patent types held by publicly funded research institutes, approximately 30 per cent of Australian patents generate *no income* to patent holders from licensing, options or assignments. Over 20 per cent generate some return of less than $250 000 annually, and some outliers can accrue over $100 million.

Assuming that the average income per active LOA held by Australian publicly funded research institutes is an adequate proxy for the direct returns to isolated human gene patents, the expected total annual revenue to Australian holders of isolated human gene patents would be between $1.6 million and $3.8 million. This is calculated by applying the average value per active LOA to the estimated number of isolated human gene patents currently held by Australian entities today.[153]

Anecdotal and confidential survey evidence on the value of selected licensing deals is broadly consistent with this estimate, which also highlights the variability of returns.

Survey research has found that upfront fees of $100 000 are often the norm for biotechnology patents with various milestone payments and around 3 per cent royalties.[154]

Stakeholder interviews held for this review suggested that most isolated human gene patents do not accrue any income. For those that do, upfront fees can be around $3 million to $5 million although they can be much higher, and milestone tranche

153 The *lower* bound value applies the average income per active LOA for MRIs ($71 495) to the *lower* bound estimate of the number of isolated human gene patents currently held by Australian entities at the 95 per cent confidence interval. The *upper* bound value applies the average income per active LOA for all publicly funded research institutes ($173 470) to the *upper* bound estimate of the number of isolated human gene patents currently held by Australian entities at the 95 per cent confidence interval.

154 Nicole, D. and Nielsen, J. op. cit., p. 121.

payments vary considerably. They are typically in the band of $2 million to $20 million or upwards of $250 million, comprised of payments for successful Phase 3 clinical trials, regulatory approval, marketing registration, and first sale in a major market. Royalties were believed to range from of 0–7 per cent of sales, depending on the product.

For publicly funded entities, financial returns to patents tend to be shared. The norm would be for around 30 per cent to be distributed to the inventor, around 30–40 per cent distributed to the research laboratory involved, and 30–40 per cent distributed to the research institution that employed the inventor.[155]

5.6 Limitations to estimates of average patent value

The average annual value of a patent may be a useful guide to use for assessing patent value, however it must be treated with considerable caution. For instance:

- there is huge variation in royalties and other income associated with LOAs, which can depend much on the licencing model in place (see box 5.5). Best practice guidelines have been developed to provide more appropriate pricing in licensing arrangements, which are set out in appendix C;
- patent value depends on who wants access to it. Many patents do not provide any royalties or other income, and their sole function is to provide indirect benefits by way of signalling to capital investors that research is unique and usable. In some cases, patent holders will withdraw a patent because the income they receive is lower than the costs of maintaining a patent. Granted patents that have ceased, accounted for 28 per cent of total isolated human gene patent and patent applications in Australia in 2012;[156]
- patent value will depend on the technology in question and its mode of evolution. For instance, it will depend on whether:
  - the technology is a broadly applicable platform technology or a specific research tool;
  - the technology is core (in which case it might not be licensed at all, or only at a high price with controls over future developments of the technology) or non-core (when licensing out for a small upfront payment is more likely);
  - the parties involved are collaborators or competitors; and
  - the relative bargaining power of the parties is even or not, which will in part reflect the financial strength and weaknesses of the parties.[157]

155 Nicol and Nielson op. cit., p. 134.

156 Based on the patent database search undertaken for this study. Ceased patents include those where the applicant chooses to abandon the patent and does no pay renewal fees.

157 Nicol, D. and Nielsen (2003), *Patents and Medical Biotechnology: An Empirical Analysis of Issues Facing the Australian Industry*, Centre for Law and Genetics, Occasional Paper No. 6, p. 119.

Price premiums for patented medicines

Another potential source of income to patent holders is any price premium obtained when successful translation of patented research results in saleable products to market.

Price premiums are widely assumed to exist by virtue of the temporary monopoly and exclusive rights that patents confer over the patented invention. However, the evidence is mixed as to whether price premiums exist between patented and non-patented medicines and diagnostics, given the large number of drivers that affect pricing outcomes.

Price premiums for first-in-class biopharmaceuticals

Intellectual property provides a limited period of exclusivity during which patented products generate high profits for the manufacturer. Once a patent expires, competition from generic products can occur. Evidence suggests that the entry of generic competition results in price declines of incumbent medicines.

One proxy of the price premium payable could be inferred from the price reduction policy for F1 medicines listed on the Pharmaceutical Benefits Scheme (PBS).[158] In 2005, the Commonwealth government introduced price measures to improve the sustainability of the PBS and take advantage of the growth in availability of generic medicines.

Among other initiatives such as staged price reductions, the price reduction policy included a 12.5 per cent reduction in prices, which is triggered by the first application to list a new brand of medicine for a medicine that was previously a 'single brand' medicine. This applies to:

- new versions of medicines where the patent for the original medicine has expired; or
- new pseudo generic medicines, which are new versions of medicines that are still on-patent, marketed by the patent holder or by another sponsor under an arrangement with the patent holder.

The inference is that the Australian government is prepared to pay an additional 12.5 per cent for first-in-class medicines relative to their generic counterpart.

More detailed analysis on the impact of generic competition on the prices of four 'blockbuster' medicines listed on the PBS suggests that the average price of four leading compounds on the PBS fell by an average of more than 30 per cent after patent expiration and the entry of generic medicines. This is based on price trends for Prozac, Losec and Zantac during the period of transition from monopoly to that of competition from the entry of generics. As shown in table 5.7, the price of originator drugs fell substantially following the entry of generics. The average prices reductions shown in table 5.8 are expressed in real terms.

Another study by the Productivity Commission used IMS data to examine the price premium for originator pharmaceutical brands compared to the cheapest generic off-patent drugs in the US. For the drugs analysed (including Ranitidine, Salbutimol,

158 Formulary 1 (F1) refer to single brand medicines. Note, this category does not include single brand medicines that are interchangeable at the patient level with multiple brand medicines.

Diazepam, Metoprolol, Ditliazem, Proxicam, Atenolol, Temazepam, Oxazepam and Betamethasone) the Productivity Commission found that the lowest generic prices were between 1.2 and 5.8 per cent of the originator brand price, with an unweighted average of 3.8 per cent.[159]

5.7 Impact of generic competition on the price of Prozac, Losec and Zantac

	Years					
	Apr-94	Apr-95	Feb-96	Feb-97	Feb-98	Feb-99
Prozac 20mg (28pack)	55.09	55.32	59.19	35.5	35.55	35.55
Number of generic competitors	0	0	1	3	3	5
	Feb-97	Feb-98	Feb-99	Feb-00	Feb-01	Feb-02
Losec 20mg (30 pack)	82.93	82.98	82.98	58.86	57.63	46.90
Number of generic competitors	0	0	1	1	1	1
	Feb-96	Feb-97	Feb-98	Feb-99	Feb-00	Feb-01
Zantac 150mg (60 pack)	33.02	33.04	26.41	24.18	23.73	23.83
Number of generic competitors	0	1	2	2	6	10

Source: The Australia Institute 2003, *A backdoor to higher medicine prices? Intellectual property and the Australia-US Free Trade Agreement*, November, p. 12-13.

5.8 Average effect on price after entry of generic competition

Years after entry of generic competition	Year 1	Year 2	Year 3	Year 4	Year 5
	%	%	%	%	%
Average adjusted price paid by PBS	-2	-27	-31	-35	-37

Note: Analysis of dispensed prices. Estimates examined price trends for Prozac, Losec, Zantac and Renitec for four years after the entry of generic competition. CPI used to adjust prices to year of generic entry.

Source: The Australia Institute 2003, *A backdoor to higher medicine prices? Intellectual property and the Australia-US Free Trade Agreement*, November, p. 13.

Price premiums for patented diagnostics

Price premiums are also expected to exist for patented diagnostics, although given the varied drivers of test costs, assessing the price premium attributable to the patent is difficult and, to a certain extent, inconclusive.

Case study evidence on price premiums for patented diagnostics

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) recently identified case studies to determine the extent to which patents and licensing practices affect the price of genetic tests. While some case studies did not yield definite conclusions due to difficulties in obtaining relevant data and challenges in determining the relative contribution of various costs to price, some did suggest that gene patents impact on licensing practices on access to, and pricing of, genetic tests (see table 5.9).

159 Productivity Commission 2003, *Evaluation of the Pharmaceutical Industry Investment Program*, Research Report, February.

5.9 Research on price premiums associated with diagnostic related patents

Genetic test	Evidence of price premium	Publication details
Canavan disease	Yes. The average price per amplicon for Canavan disease is $199.58 as opposed to$111.50 (for unlicensed Tay Sachs test.	Colaianni, A. Chandrasekharan, S. and Cook-Deegan, R. 2010, Impact of gene patents and licensing practices on access to genetic testing and carrier screening for Tay-Sachs and Canavan disease, Genetics in Medicine, vol. 12, Issue 1s, April, S5-S14.
Hearing Loss	No.	Chandrasekharan, S. and Fiffer, M. 2010, *Impact of gene patents and licensing practices on access to genetic testing for hearing loss*, Genetics in Medicine, vol. 12, Issue 1s, April, S171-S193.
Cystic Fibrosis	Yes. Initial license fee for kit licenses and the in-house commercial test is $25 000 and$15,000 respectively. The kit licence also involves a royalty equal to 3.6 per cent of net sales of products.	Chandrasekharan, S. Heaney, C. James, T. Conover, C. and Cook-Deegan, R. 2010, *Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis*, Genetics in Medicine, vol. 12, Issue 1s, April, S194-S211.
Hereditary Hemochromatosis	Yes. Licensing involves upfront payments and a per test fee of $20.	Chandrasekharan, S. Pitlick, E. Heaney, C. Cook-Deegan, R. 2010, *Impact of gene patents and licensing practices on access to genetic testing for hereditary hemochromatosis*, Genetics in Medicine, vol. 12, Issue 1s, April, S155-S170.
Spinocerebellar ataxia	Yes. Highest cost of testing for all genetic tests of up to $7300 for a panel test.	Powell, A. Chandrasekharan, S. Cook-Deegan, R. 2010, *Spinocerebellar ataxia: Patient and health professional perspectives on whether and how patents affect access to clinical genetic testing*, Genetics in Medicine, vol. 12, Issue 1s, April, S83-S110.
Alzheimer's Disease	Inconclusive.	Skeehan, K. Heaney, C. and Cook-Deegan, R. 2010, *Impact of gene patents and licensing practices on access to genetic testing for Alzheimer disease*, Genetics in Medicine, vol. 12, Issue 1s, April, S71-S82.
Long QT syndrome	Yes. Prior to 2009 where there was one licensee, the cost was $74 per amplicon by FAMILION panel as opposed to $34 per amplicon for BRCA1 testing. Since 2009 there are two licensees — PGxHealth offers testing for 11 genes, and the price remains at $5400. GeneDx tests for 10 genes and charges $2500 for index cases.	Angrist, M. Chandrasekharan, S. Heaney, C. and Cook-Deegan, R. 2010, *Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome*, Genetics in Medicine, vol. 12, Issue 1s, April, S111-S154.

Source: The CIE, based on the publications mentioned.

Many of these case studies have been drawn upon in submissions to the various isolated human gene patent inquiries that have been held over recent years, which also point to different manifestations of the impact of exclusive rights on patents underpinning diagnostic tests.

- *Cystic Fibrosis (CF).* Genetic testing for CF is non-exclusively licenced for a) CF testing 'kit' developers including companies that develop and sell genetic CF testing kits, and b) laboratories that wish to develop their own 'in-house' CF assays for testing patient samples at a single site laboratory. The initial license fee for kit licenses is $25 000 while the initial license fee for the in-house commercial test is $15 000. The kit licence agreement also dictates that licensees must agree to pay royalities that are effectively equal to 3.6 per cent of their net sales of products. Revenue obtained from these fees

and royalties have gone, in large part, toward covering the costs for international patent protection.

- *Canavan disease.* The developers of this genetic test used their patent to establish restrictive license conditions and sought license fees that exceeded what laboratories offering similar tests for Tay-Sachs disease were willing to pay. Following litigation against the patent holder, which resulted in a confidential settlement that altered the license terms in a way that the plaintiffs apparently considered acceptable, there remained an average price difference. The case study concludes that 'the average price per amplicon for Tay-Sachsis $111.50 while the price per amplicon for Canavan disease is $199.58'.[160] The price differential is likely to reflect a number of factors including that of the patent.
- *Long QT syndrome (LQTS).*The 5-gene version of FAMILION LQTS testing costs US$5400 per index case (a full-sequence test to look for mutations) or US$74 per amplicon. The policy significance of LQTS intellectual property came to the fore through the 2007 Congressional testimony of Bio-Reference Laboratories CEO, Dr Marc Grodman, and Columbia University clinical geneticist, Dr Wendy Chung. They suggested that a competitive laboratory could offer the test for about 'a quarter of the price'. Further, the test would be accessible to many more patients if it were 'correctly' priced in a competitive marketplace. Researchers compared the LQTS testing price to benchmarks and found that it was nearly twice the US$38-per-amplicon cost of hereditary breast cancer testing (albeit at a much lower volume), but significantly less expensive than the US$129-per-amplicon partial test that was offered in 2002 and the per-amplicon price of some other tests (for instance, hearing loss and Tay-Sachs/Canavan). The researchers concluded that 'a competitive presence could have accelerated the test to market and lowered the cost from $5400'.
- *Hearing Loss.* Mutations in several genes have been implicated in genetic hearing loss. While most hearing loss genes identified to date are not patented, *GJB2* gene patents have been exclusively licensed by Athena Diagnostics. The majority of laboratories currently providing tests for genetic hearing loss are academic health centres. Prices for *GJB2* full-sequence analysis range from US$140 to US$430 per amplicon. Athena charges US$472 to US$575 for *GJB2* testing.

  Further hearing loss genetic tests including *GJB2* and *MT-RNR1*, which are patented, and *GJB6*, *SLC24A6*, and *MT-TS1*, which are not patented, have been developed and are offered by several providers at similar prices. Costs of hearing loss tests do not appear to correlate strongly with patent status. For instance, the price of the most expensive test can be attributed mostly to the costs of sequencing a large gene.
- *BRCA1 gene testing.* In 2001, screening the BRCA1 gene for mutations cost between $1200 and $2000 for complete gene sequencing in Australia. The comparable cost for testing by Myriad, which would be performed at laboratories in the US, was US$2400. Given exchange rates at the time, the Australian Health Ministers' Advisory Council (AHMAC) estimated that the price differential was two to three times higher than testing within Australia.

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160 Secretary's Advisory Committee on Genetics, Health, and Society 2010, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests,* April.

The AHMAC Working Group on Human Gene Patents estimated that over 1000 BRCA1 tests were provided in the year 2000, representing a cost of $1.2 to $2 million but a projected cost of $4.5 million for full sequencing of these genes by the commercial company.[161]

- *IgH and TCR gene rearrangements.* These are commonly performed on cancer tissue from patients with lymphoproliferative disorders or acute myeloid leukaemia. A significant amount of diagnostics offered by Invivoscribe is underpinned by Australian innovation, The Australian company Monoquant has multiple pending applications[162] and have exclusively licensed these to Invivoscribe. In 2006, there were approximately 4000 IgH and TCR tests performed in Australia using either an in-house method or a commercial kit sold by the patent holder — Invivocribe Technologies. The company approached all Australian laboratories which performed such tests and insisted that they:
  - confirm that they are testing exclusively with the company's kit and according to the company's method;
  - confirm they have switched to exclusive use of the company's kit and method; or
  - obtain a sub-license from the company to use their own in-house tests.

  The cost of performing an in-house test is approximately $28 per patient (excluding labour, on-costs, and validation costs apportioned over each test). The cost of performing the test using the company's kit is approximately $292 per patient (excluding labour). Tests are not rebated by Medicare, and it is likely that the cost would be borne by either the public hospital or the patient. The sub-license cost is not known, but laboratories reportedly switched to purchase the kit in preference. Some laboratories ceased to perform testing, choosing to refer to other laboratories; others triaged their patient referrals for testing more actively.[163]
- *Cytochrome P450 gene.* Prior to 2005, genetic testing of the cytochrome P450 gene was provided by Australian laboratories for approximately $250. Genetic errors in this gene can have a significant impact on the metabolism of some common medications. In 2005, the exclusive licensee for the cytochrome P450 gene — a UK-based company called LGC — sought to enforce its rights by licensing laboratories offering the test. There was to be an initial fee of £20 000 plus 5 per cent of any fees for tests performed. If these costs were amortised over a five-year period, the test cost would have risen by 500 per cent. The situation was untenable and some laboratories ceased offering the test in Australia. In 2006 after these letters of demand received, there were

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161 The AHMAC Working Group on Human Gene Patents suggest that payment of higher high royalties or full testing costs would force clinicians to reprioritise their testing, either reducing the number of breast cancer tests provided, maintaining existing breast cancer testing levels at the expense of other genetic tests or judging the expense prohibitive to offering testing. Otherwise, a significant increase in public funding would be required to cover the estimated 2-3 fold increase in test prices.

162 2009238365, 2008316288, 2010256347, these applications are listed as 'filed' and all claim method only, except 20082555569 claims a partial sequence and method claims.

163 Royal College of Pathologists of Australasia 2010, Response to the Senate Community Affairs Committee Inquiry into Gene Patent.

only 140 assays (tests of this gene performed nationwide).[164] The relevant Australian patent for this test has now expired.[165]

Broader data sets are less conclusive

These case studies show that examples of price premiums being applied to genetic diagnostic tests can and do arise. However, this is not always the case, and broader examination of the data is less conclusive.

The Department of Health and Ageing (DoHA) commissioned the Royal College of Pathologists of Australasia (RCPA) to perform a survey on genetic testing in Australia in 2007 and 2011. According to the 2011 survey there are over 500 molecular genetic tests available in Australia performed by 39 laboratories. The most common targets (genes) within molecular genetics are HFE (Hereditary Haemochromatosis), F2 (Thrombinemia), F5 (Thrombophilia, Factor V Leiden), CFTR (Cystic Fibrosis) and BCR-ABL (Chronic myeloid leukaemia amongst other diseases).[166]

Genetic testing is complex, and mutations in one gene can be the cause of multiple diseases. Furthermore, diseases can be caused by mutations in a few different genes. Genetic tests in Australia are provided by hospitals and private diagnostic facilities. The prices charged vary between service providers, making price comparisons (with and without patents) difficult.

One option for eliminating price variation is to examine tests that are reimbursed by the MBS, as shown in table 5.10. Unfortunately there are too few genetic tests where it can be confident that the test is underpinned by any particular patent to draw any firm conclusions. Of the 14 tests performed in Australia under the MBS only two appear to have both a U.S. patent and an Australian patent, three had a U.S. patent but no Australian one, and nine had no patents.

5.10 Medicare Benefit Schedule (MBS) price of genetic tests and patent

Genetic Test	MBS	US and Australian patent	US Patent	No Patent	Price
					$
Thrombophilia	73308	✓			36.45
Haemochromatosis DNA studies	73317	✓			36.70
Von Hippel-Lindau syndrome	73333		✓		600.00
Charcot-Marie-Tooth Neuopathy Typ1 1A- Mutation Testing -Genotyping	73294		✓		230.95

(continued on next page)

164 Royal College of Pathologists of Australasia 2010, Response to the Senate Community Affairs Committee Inquiry into Gene Patent.

165 Patent AU 642705 expired on the 17th of January 2011.

166 Royal College of Pathologists of Australasia 2012, *Report of the RCPA Genetic Testing Survey 2011*, December.

Genetic Test	MBS	US and Australian patent	US Patent	No Patent	Price
					$
Fragile X mental retardation 1 screening – Genotyping	73300		✓		102.00
Gene Rearrangements-APML-Genotyping	73314			✓	230.95
Detection of HLA-B27 (autoimmune disorders)	73320			✓	40.55
Detection of HLAB5701 prior to initiation of Abacavir therapy	73323			✓	40.55
JAK2 Mutation Analysis- Genotyping for V617F mutation	73325			✓	74.50
Gene Rearrangements-FIP1L1-PDGFRA-Genotyping	73326			✓	230.95
Pharmacogenetics: Thiopurine S-methyltransferase	73327			✓	51.95
EGFR Mutations test	73328			✓	397.35
KRAS Mutations Testing	73330			✓	230.95
HER2 ISH test for trastuzumab therapy	73332			✓	315.40

Note: It is difficult to determine if a patent underpins a particular genetic test. These prices are correct as of the 14th of February 2013. http://www.health.gov.au/internet/mbsonline/publishing.nsf/Content/Medicare-Benefits-Schedule-MBS-1.

Source: The CIE.

To draw on a broader data set, patent information was collected for 37 genetic tests that had readily available pricing information. This shows possibly stronger evidence of a price premium for tests over which there is a patent, although this analysis does not distinguish between patents that are still in force or no longer in force and whether the patent rights are enforced by the patentee. The median and average cost of genetic tests in the sample is higher in tests that have an Australian patent (8 tests). However, the minimum cost of tests regardless of patent status was similar (see appendix C for additional patent information).

5.11 Pricing data for a sample of non MBS listed genetic tests

	Patent (U.S and Aust.)	Patent (U.S)	No Patent
	$	$	$
Median	899.00	235.00	275.00
Mean	1060.80	285.64	345.61
Max	2950.00	800.00	1 567.25
Min	75.00	80.00	80.00

Note: Patent (U.S and Aust.), n=5. Patent (U.S), n=14. No Patent, n=18. Pricing information found on diagnostic facility brochures and websites, which may be out-dated. Patent information was difficult to determine for all genetic tests, as some tests listed as not having a patent might have a certain mutation covered.

Data source: The CIE.

As is the case with therapeutics, patents are just one factor attributable to the cost of a genetic test. Other factors include the 'size' of the gene, sometimes it is better to look at cost per amplicon.[167] Also, some genetic tests involve multiple genes, for example, the test for Long QT syndrome is patented and can be tested as part of a panel (six genes), and can cost up to $2950.

'Attracted' investment for human genetic research

As estimated in chapter 2, approximately $795 million is invested in human genetics research annually, but only a proportion of this investment will have any interface with the patent system, and even less would be genuinely attributable to the security of a patent.

For instance, this review has found most human genetic research funded in Australia is more akin to basic research where inventions are yet to be identified and research is often published and widely disclosed.

Innovation, and investment in innovation, by universities and MRIs is not significantly 'attracted' by patents

Only a small proportion of human genetics related research undertaken by universities and MRIs would result in a patent, and only a small proportion of these patents would be out-licenced or otherwise transferred to a company involved in downstream commercialisation and product development.

Survey evidence from Nicol and Nielsen (2003) found that patenting is *not* the norm and that while researchers can feel pressure to generate income, causing lots of patents to be filed, licensing income from patents is low, with about a 2 per cent return on investment.[168]

Stakeholder interviews held as part of this study found that among upstream researchers, patents are unexpected and beneficial to have, but do not drive research behaviour, and returns from patents complement but do not substitute any other funding sources.

That said, there are some elements of upstream research that would be more directly affected to patents. This would be likely to include:

- research funded from commercial sources, which would be attracted by the presence or potential presence of a patent, which may be the continuation of existing research that might otherwise have stopped; or
- research which has been funded, at least partly due to existing patents held by the applicant which has signalled the quality of the research candidate. Many of the research organisations interviewed as part of this study believe that venture capital is very much influenced by patents held by Australian biotechnology companies.

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167 Amplicon is a piece of DNA or RNA that is the result of artificial amplication, for example by PCR.

168 Nicol and Nielsen op. cit., p. 131.

Moreover, when inventions are made by universities and MRIs, patents become important commercial bargaining tools, and research institutes are becoming increasingly savvy in lodging provisional patents in anticipation of later engagement with commercial partners.[169]

Investment by upstream biotechnology companies is largely patent-dependent

Commercial partners are disinclined to invest in biotechnology, and generally will not invest in the development of biotechnology if:

- access to a genetic technology cannot be guaranteed, which typically involves access to a recombinant (modified) DNA technology patent, and in some cases also an isolated human gene patent; and/or
- there is any uncertainty about the ownership of the intellectual property that is tied to the technology.

Hence, the technology transfer that occurs in the commercialisation of human genetic research typically requires the institutional framework of patents.

The cumulative nature of biotechnology research means that IPR needs to be assembled in order to develop a platform, with survey evidence suggesting that 'it is common to have to license-in three patents in order to get one patent out'.[170]

Pharmaceutical and biotechnology companies involved in downstream product development, patents (usually recombinant DNA patents and sometimes isolated human gene patents) are essential for the recovery of research and development expenditure, and to ensure that there is an adequate incentive to invest in the industry.

While this study focuses specifically on isolated human gene sequence patents, it is recognised that there are linkages between isolated human gene patents and other gene patents involving modified or recombinant human DNA technologies, which together occupy the human genetics research effort in Australia.

Chart 5.12 provides a breakdown of the distribution of pharmaceutical and biotechnology R&D in Australia across the research continuum , with approximately 40 per cent of privately funded R&D expenditure in Australia by Australian firms or Australian subsidies relates to work contracted to or undertaken in collaboration with hospitals, which by and large would be post the pre-clinical research phase.

Over 80 per cent of privately funded R&D expenditure in Australia by Australian subsidies on behalf of their global parent relates to work contracted to or undertaken in collaboration with hospitals or other pharmaceutical companies, which again would be highly translational research.

Virtually all of the private funded R&D in Australia directly by global companies relates to later stage clinical trials (phase 3) and beyond into manufacturing and processing

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169 Many research institutes will only take patents to the provisional phase because they are not well enough resourced to take them further.

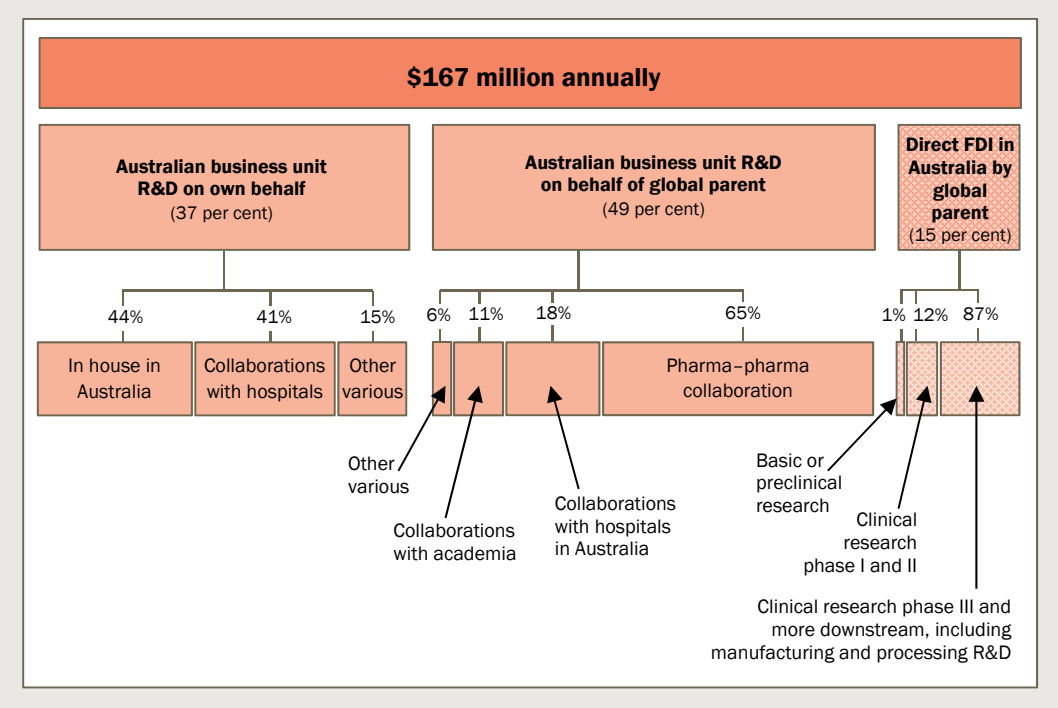
170 Nicol and Nielsen op. cit., p. 110.

R&D, which is directly related to the later stages of getting products to market (to the Australian market and for export).

It is not possible to identify how much of the private R&D effort in human genetics is underpinned by isolated human gene patents as opposed to recombinant or modified DNA technologies. .

However, it is likely that all direct FDI at least is most dependent on upstream patents, be they isolated human gene patents or not, because of the important role of patents in the providing confidence to international investors in Australia.

5.12 Pharmaceutical and biotechnology business expenditure on R&D in Australia



Data source: Medicines Australia 2010, op. cit. and the CIE

Health benefits and value

Estimating the health benefits of human genetic technologies is difficult, arguably impossible, to do in any direct sense.

It depends on:

- the importance of patents to innovation and ultimately access to new medicines and diagnostics predicated on human genetic technologies; and
- the extent to which new treatments are the best and most cost effective that they can be, which reflects:
  - the impact of patents on other, potentially restricted, research; and
  - the commerciality of bringing improvements or refinement to patented medicines to market, which could potentially be negated by patents.

There are also likely to be lengthy lags between the patent, the commercialised products, and then improved health outcomes.

Clearly adverse health conditions are costly. The Australian Institute of Health and Welfare has estimated that total health and aged care spending in Australia will rise to $246 billion in 2033, up from $85 billion in 2003. Expected spending by disease group is shown in table 5.13, which also highlights those diseases that are already the focus of considerable investment in human genetic technologies.

5.13 Projected health and residential aged care expenditure by disease group, 2002–03 to 2032–33

	Expenditure (millions of 2006–07 dollars)				Change 2002–03 to 2032–33 (per cent)
	2002–03	2012–13	2022–23	2032–33	
Cardiovascular	9 329	12 535	16 781	22 559	142
Respiratory	7 188	9 679	14 483	21 947	205
Injuries	6 650	8 134	10 555	14 353	116
Dental	5 888	7 705	10 766	14 925	153
Mental	5 147	6 670	8 998	12 109	135
Digestive	4 877	6 916	10 612	16 488	238
Neurological	4 727	7 358	12 095	21 560	356
Dementia	3 847	6 033	9 889	17 837	364
Parkinson's disease	323	488	825	1 399	334
Other neurological	557	837	1 380	2 325	317
Sense disorders	2 636	3 642	5 640	8 859	236
Musculoskeletal	4 411	6 289	9 567	14 234	223
Genitourinary	3 678	4 966	7 272	10 857	195
Cancer	3 487	5 128	7 807	10 112	190
Endocrine, nutritional and metabolic	2 584	3 322	4 602	6 395	147
Skin	2 373	3 309	5 012	7 767	227
Maternal	2 150	2 427	3 167	3 953	84
Infectious	1 890	2 427	3 359	4 673	147
Diabetes	1 607	2 831	5 007	8 610	436
Type 2 diabetes	1 296	2 427	4 495	8 041	520
Neonatal	631	724	952	1 185	88
Congenital	310	369	492	633	104
Other	15 500	21 041	30 564	44 837	189
Total health and residential aged care expenditure ($m)	85 063	115 471	167 729	246 056	189
GDP ($bn)	919	1 235	1 582	1 981	
Total as per cent of GDP	9.3	9.3	10.6	12.4	

Most relevant to existing human genetic technologies.

Source: Australian Institute of Health and Welfare 2008, Projection of Australian health and aged care expenditure by disease, 2003 to 2033, http://www.aihw.gov.au/publication-detail/?id=6442468187.

There is also a considerable body of literature that has sought to identify specific types of health costs associated with conditions that are the focus of human genetics research, such as genetic disorders, as well as quantify the health and medical costs associated with

health disorders, or cost savings associated with improved therapies and treatments as a result of better treatment.[171]

Timeliness of access to medicines

One of the potential connections between isolated human gene patents and health outcomes is the impact of patents on timely access to innovative medicines in Australia.

There are many factors that drive time-to-country market outcomes for innovative medicines. Many stakeholders refer specifically to recorded differences in the availability of new medicines between Australia and New Zealand, with Australia faring far better, due primarily to a more favourable reimbursement system for pharmaceuticals.

Research shows that if a new medicine is reimbursed in New Zealand, it occurs, on average, approximately 14 months after it is reimbursed in Australia. This has caused tension in New Zealand where consumers are believed to be denied access to a large and broad number of innovative new medicines when compared to their Australian counterparts.[172]

While there was no examination of differences in the IPR regime, the broader point is that factors that impact on the commercial return of innovative medicines can and do have an impact on in-country access to leading treatments.

Other research has shown that a country's choices regarding how to protect pharmaceutical innovation can have a significant impact on:

- whether drugs are launched; and
- how quickly they are made available to domestic consumers.[173]

Still, the IPR regime is just one of several important factors that influence the availability of innovative medicines and diagnostics in a particular market. As shown previously in chapter 4, commercial imperatives 'reign supreme'. Hence, even where patent rights are

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171 See World Health Organisation, http://www.who.int/topics/global_burden_of_disease/en/, Australian studies such as Brameld, Maxwell, Dye, O'Leary, Goldblatt, Leonard, Bourke, and Glasson, Measuring the impact of genetic disease in the WA population. http://www.genomics.health.wa.gov.au/publications/docs/Measuring_the_impact_of_genetic_disease.pdf, or various examples of potential health care cost savings associated with disease modifying therapies http://www.sciencedirect.com/science/article/pii/S0149291811003031.

172 Wonder, M. (2006), Access by patients in New Zealand to innovative new prescription-only medicines; how have they been faring in recent times in relation to their trans-Tasman counterparts?, Novartis.

173 Lanjouw, J. 2005, Patents, Price Controls and Access to New Drugs: How Policy Affects Global Market Entry, Agricultural and Resource Economics Department, April. Lanjouw found that a high-income country spurs market entry and increases the probability that new drugs are available to its consumers quickly by offering at least short-term protection to pharmaceutical products. Long–term patent protection was also found to make a positive contribution to availability in this context. However, for the low and middle-income countries there is mixed evidence as to whether extending protection enhances access to new pharmaceuticals.

assured, there continues to be scarce research into brain or other rare cancer therapies, where the consumer market is relatively small.

The promotion or hindrance of other research

The simultaneous purpose of patents is to both incentivise innovation and spur the innovation of others. Quite aside from the intention to share the cost risks of innovation, patents create a market for innovation as rival firms or researchers 'design around' the innovation, and the patenting process shares and disseminates information about breakthrough technologies.

Stakeholder interviews undertaken during this review suggest that patents are often effective at spurring innovation. Researchers are often encouraged to review patent records, or the content of patents is reviewed in published literature.

Many of the stakeholders interviewed as part of this study contend that patents are a 'positive' for research:

- patents are part of the reward and recognition structure for effort;
- the holding of patents is seen to be positively associated with access to Commonwealth competitive grant funding for medical research; and
- patents are a useful form of information dissemination, with several MRIs commenting that they wish their researchers would make even more use of patent database searchers to inform research directions.

There was no evidence provided to this review that patents adversely affect research or that research independence is compromised by patents, particularly given the research exemptions afforded by the *Raising the Bar Act*.

As acknowledged:

> If patent protection were not available, innovators might resort to secrecy to protect others from using their inventions. Such secrecy may impede the diffusion of knowledge and hinder follow-on innovations. One advantage of patents is that they require public disclosure of the invention, which may in itself spur follow on discoveries.[174]

However, the case studies highlighted previously suggest that patents have the potential to influence research direction, and at the very least can eliminate the opportunity for market competition to drive efficiency and quality control for those that hold isolated human gene patented technologies.

Evidence on the impacts of patents on the direction of research

Research by the Intellectual Property Research Institute of Australia (IPRIA) used data from 3000 academic scientists to gauge whether the presence of patents in a particular research area shapes scientist's decisions about the direction of their research.

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174 Patricia M. Danzon, P. Nicholson, S. 2012, *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, Oxford University Press, April.

Approximately 47 per cent of all respondents report their choice of research projects has been affected by the presence of other parties' patents.[175]

While the study concluded that transaction costs and the culture of the workplace have the largest influence over whether or not patents affect the direction of research, scientists' understanding of patent law, their recent experience seeking permission to use patented material, and the source of research funds can also be significant.

IPRIA found that it possible that patents could lead 'non-patenting' scientists into areas of inquiry that are free(er) of patents, possibly, further into the realm of esoteric, abstract science where there are no (or fewer) patents, while at the same time driving the 'patenting scientists' further into research with potential commercial value.

Impacts on research delays and restrictions

Despite research exemptions in the *Raising the Bar Act*, many stakeholders remain concerned that patent rights over upstream inventions can undermine the advance of biomedical research by delaying research. Key concerns are that:

- some patents are considered to cover 'foundational' inventions, where innovation should be broadly and widely encouraged given its important application. Examples of foundational patents that highlight this concern include recombinant DNA, PCR and Taq polymerase, embryonic stem cells, and genes and gene applications;
- concerns exist regarding the 'breadth' of patents, where there is the potential for broad interpretations to be made of a patent that could deter downstream researchers from researching in what they consider to be a broad area of research; and
- there are concerns that reach-through rights to future inventions can deter subsequent innovation, such as a right to a compound that acts on a patented target even though the compound itself is not described in the patent claims.

Even the uncertainty created around issues of interpretation is seen to potentially inhibit research in an area where researchers are concerned about how a patent claim may be interpreted.[176]

These concerns are arguably elevated with respect to medical devices and diagnostic tests because the regulatory requirements for them are far less onerous than for therapeutics, and some may argue that the risks, time and expenses involved in the drug approvals process are not as significant a consideration for devices and diagnostics.

This may particularly be the case for diagnostic tests, as once the isolated gene sequence for a particular disease related gene has been identified and isolated, the development of

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175 Webster, E. Jensen, P. 2010, *Do patents alter the direction of scientific inquiry? Evidence from a survey of academic scientists*, Intellectual Property Research Institute of Australia, Working Paper No. 5/10, November.

176 Walsh, J., Arora, A. and Cohen, W. (2003), 'Effects of Research Tool Patenting and Licensing on Biomedical Innovation' in Cohen, W. and Merrill, S. (eds), Patent in the Knowledge-based economy, National Academies Press, Washington, pp. 296–297.

the test is not particularly onerous.[177] Case studies mentioned earlier highlight real instances where patented diagnostics have led to high prices and potentially compromised outcomes in terms of test quality and validation.

While there is conjecture about the impact of isolated human gene patents on delays in testing, research institutes and public hospitals consulted as part of this review failed to substantiate that testing delays specific to patents have occurred. This includes the often mentioned delay in BRCA1 and BRCA2 testing when GTG was seeking to enforce its patents, prior to its decision to withdraw its patents from the Australian market.

Empirical evidence is mixed, with some studies pointing to impacts of patents on research direction and activity, and some not.

For instance, MIT researchers utilised data on the sequencing of the human genome by the public HGPoject and the private firm Celera to estimate the impact of Celera's gene-level IP on subsequent scientific research and product development. Genes initially sequenced by Celera were held with IP for up to two years, but moved into the public domain once re-sequenced by the public effort.

Across a range of empirical specifications, the study concluded that Celera's IP led to reductions in subsequent scientific research and product development on the order of 20 to 30 per cent. The author notes that:

> these results suggest that Celera's short-term IP had persistent negative effects on subsequent innovation relative to a counterfactual of Celera genes having always been in the public domain.[178]

The RCPA supports the view that a patent holder can block further developments of a genetic test, which is inappropriate when providing testing to different ethnic groups because the frequency of certain genetic errors can vary widely. For instance, Myriad Genetics provided a test that sequenced every nucleotide in the two genes causing breast cancer susceptibility but this method failed to detect certain types of errors (called deletions) in these genes. A supplementary method was described by research scientists that would detect gene deletions, but for a number of years Myriad Genetics did not include this additional assessment in its testing. Other laboratories could not offer the supplementary test because they were not licensed to analyse the genes.

> Effectively the patent blocked the delivery of supplementary testing that would increase the accuracy and usefulness of the investigation. As a result, women were being incorrectly advised that there was no identifiable mutation in their genes, and that genetic testing in the family was impossible. Approximately 12% of women reported by Myriad Genetics to have normal BRCA1 and BRCA2 genes in fact had a deletion.[179]

However, there is not necessarily evidence that patenting and licensing activities reduce the volume of a genetic test. The Cytochrome P450 genetic test is licensed to LGC who

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177 Nicol and Siemen op. cit. p. 61.

178 Williams, H. 2012, *Intellectual property rights and innovation: Evidence from the human genome*, MIT Department of Economics and NBER, May.

179 Royal College of Pathologists of Australasia 2010, Response to the Senate Community Affairs Committee Inquiry into Gene Patent.

enforced their rights in 2006. However, despite the increase in test costs with licence fees payable, there were 140 tests performed in 2006 and a much higher 280 tests performed in 2007.[180]

Direct financial costs of patents

Applying for, and maintaining, a successfully approved patent, can be costly for patent applicants and patent holders.

Given the high failure rates towards the downstream end of the research-development continuum, these costs can outweigh patent value and comprise an inefficient cost or misallocation of resources.

Costs include the direct application and renewal costs and enforcement costs.

Application and renewal

Applying for and maintaining a patent requires payment of patent attorney fees and fees payable to IP Australia associated with applications, renewals, oppositions and hearings.

A summary of application fees is provided in appendix E.

The average actual term of standard biotechnology patents (the period during which the patent holder continues to pay renewal fees) is approximately 12 years, which is higher than the average actual term for standard patents generally, which is approximately eight and a half years.[181]

In aggregate, it has been estimated that the cost of an Australian standard patent including attorney fees is usually between $8000 and $12 000 and annual maintenance fees over a 20 year term can add a further $8000 to the cost.[182] For a portfolio of patents, costs can often run into the hundreds of thousands annually.

Several of the research institutes and public hospitals interviewed as part of this study noted that patent maintenance costs can draw substantially on their resources, particularly for entities like hospitals running on low operating budgets.

These costs are often a factor in decisions to withdraw a patent if there is no imminent opportunity to transfer the technology to a company further downstream.

Research institutes do not receive specific funding for the maintenance of a patent portfolio, which heightens the opportunity cost to institutes of inefficient or unnecessary patenting.

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180 Royal College of Pathologists of Australasia 2008, Report of the RCPA Genetic Testing Survey 2008.

181 IP Australia, Submission P56 to Australian Law Reform Commission 2004, *Genes and Ingenuity: Gene patenting and human health*, 4 November 2003.

182 IP Australia.

Research institutes have also been known to hurry into decisions to partner with a downstream company over a provisional patent because they do not have the financial resources to take the patent beyond the provisional phase.[183]

Costs of patent enforcement on impact on patent value

The more substantial cost of patents is the cost of enforcement, which again often disincentives research institutes, and in some cases companies, from patenting.

In the case of companies, concerns about enforcement costs can lead to alternative approaches to protecting the intellectual property of human genetic technologies through trade secrets, because 'patents are only as good as your defence of them.'[184]

The costs of patent enforcement will depend on:

- the integrity of the IPR regime in a particular market, including the presence or absence of infringement proceedings and other enforcement activities related to isolated human gene patents;
- levels of awareness of the patent rights; and
- the availability of skills and expertise of organisations and firms to negotiate commercially viable licences with patent holders to allow for the development of alternative technologies in relation to an already patented gene without uncertainty around ownership.

Patent enforcement, particularly for diagnostics, has been a much greater issue in the United States and other major international markets, whether there is evidence that patent and licence holders are enforcing their right to exclude non patent or licence holders from performing genetic tests.[185]

There is a variable record of patent enforcement in Australia, which is intrinsically more difficult with respect to diagnostics. For many tests, patent holders in Australia have not aggressively enforced their rights against providers of testing facilities (and BRCA1 and BRCA2 tests have been withdrawn in Australia although they remain restricted in larger overseas markets where litigation over the patent remains ongoing).

A 2012 survey of genetic testing laboratories in Australia found that only 12.5 per cent of respondents had paid licence fees or royalties (other than those included in the price of a commercial kit) to provide genetic tests.

This is down from 36 per cent of respondents surveyed in 2002–03, when 82 per cent of fees paid related to polymerase chain reaction (PCR) methodology for amplifying DNA, which has since expired.

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183 Nicol and Nielsen, op. cit., p. 131.

184 Respondent to survey by Nicol and Nielsen, op. cit., p. 77.

185 For instance, see Cho, M. Illangasekare, S., Weaver, M., Leonard, D., Merz, J. (2003), Effect of Patents and Licences on the Provision of Clinical Genetic Testing Services', *Journal of Molecular Diagnostics 3.*

Just 12.5 per cent of respondents said that they had received notifications since the start of 2010, down from 26 per cent reporting receipt of a notification in the 2002–03 survey, again all with respect to PCR.[186]

Often clinical geneticists in the public health system are unaware and/or unperturbed by the existence of patentable material. Public entities commonly do not pay licencing fees or observe patents given the belief that they are unlikely to be prosecuted due to uncertain legal grounds, the costs of pursuing litigation and subpoenaing records, and the usual geographical isolation of patent holders.

A lack of awareness and non-compliance with commercial patents has also been cited in the literature.[187] However, commentators suggest that this does not provide a sustainable solution in the long run.

> Especially in the era of establishing standards for genetic testing, it appears necessary to raise awareness on patent matters. Moreover, worldwide efforts to harmonize and standardize genetic testing require a way to practice genetic diagnostics legitimately, without violating IP rights, in line with recommendations made by the OECD and the ESHG.[188]

The impact of restrictions to competition on test quality

Concerns have been raised about the extent to which exclusive rights holders are incentivised to develop and provide quality genetic testing services.

The AHMAC Working Group on Human Gene Patents have raised concerns that business models focused on licencing technology to a single private company would lead to a loss of expertise from Australian public sector laboratories and lost opportunities for further clinical innovation or discovery.

In 2006, commentary in the *Journal of the American Medical Association* questioned the quality of Myriad Genetics' test for breast cancer susceptibility, pointing to its inability to detect genomic rearrangements, insertions, and deletions. The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) also cites the LQTS case study, which takes a similar view, concluding that more competition might have brought about greater progress in understanding the complicated genetics of familial LQTS. Greater understanding of the disease, in turn, would improve testing for the disease.[189]

In general, many stakeholders argue that the quality of genetic testing for a condition improves when there are multiple providers. For instance, the Royal College of Pathologists of Australasia (RCPA) submitted to the 2010 Senate Inquiry into Gene

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186 Nicol. D. and Liddicoat (2012), 'Do Patents Impede the Provision of Genetic Tests in Australia?', Law Faculty, University of Tasmania, awaiting publication.

187 Gaisser, S. Hopkins, M. Liddell, K. Zika, E. Ibarreta, D. 2009, *The phantom menace of gene patents*, Nature Vol. 458 pp. 407–408.

188 Berthels, N. Matthijs, G. and Overwalle, G. 2011, *Impact of gene patents on diagnostic testing: a new patent landscaping method applied to spinocerebellar ataxia*, European Journal of Human Genetics, online publication pp.1-8.

189 Secretary's Advisory Committee on Genetics, Health, and Society 2010, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests,* April.

Patents that reviewing the performance of diagnostic testing is best achieved through benchmarking performance and independent assessment of external quality assurance. Where a monopoly on providing a genetic test exists, this eliminates opportunities for collaboration and removes a key mechanism for identifying errors.[190]

Empirical studies have been conducted which suggest that patents and licenses have hampered the development of, and access to, genetic testing services. A survey of US clinical laboratory directors that perform DNA-based genetic tests concluded that patents curtailed the provision of genetic testing services.[191]

- 25 per cent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Further, 53 per cent of respondents reported the decision not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories.
- The survey found that 22 patents that were relevant to the performance of these 12 tests. Fifteen of the 22 patents (68 per cent) were held by universities or research institutes, and 13 of the 22 patents (59 per cent) were based on research funded by the US Government.

Overall, respondents reported that their perceptions of the effects of patents on the cost, access, and development of genetic tests, or data sharing among researchers, were negative.[192]

It is also suggested that restricting testing to one laboratory inhibits the training and development of next generation laboratory scientists and limits the number of knowledgeable individuals who can assist in the diagnosis and management of at-risk patients. Once the genes from a patient have been analysed, the pathologist must interpret 20 000 different results and determine whether a particular genetic variation is causing disease or is simply a benign variation. The professionals performing this work gain skills that are immediately applicable in other areas of genetic testing.

Assessing the net impact of patenting isolated human genetic technologies

It is not possible to 'count up' the benefits and costs of isolated human gene patents, although some of the economic impacts can be broadly estimated.

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190 Royal College of Pathologists of Australasia 2010, Response to the Senate Community Affairs Committee Inquiry into Gene Patent.

191 A telephone survey was performed in 2001 of all laboratory directors in the United States who were members of the Association for Molecular Pathology or who were listed on the *GeneTests.org* website. 58 per cent of 211 laboratory directors' responses were included in the data analysis.

192 Cho, M. Illangasekare, S. Weaver, M. Leonard, D. Merz, J. 2003, *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, Journal of Molecular Diagnostics, Vol 5(1), February.

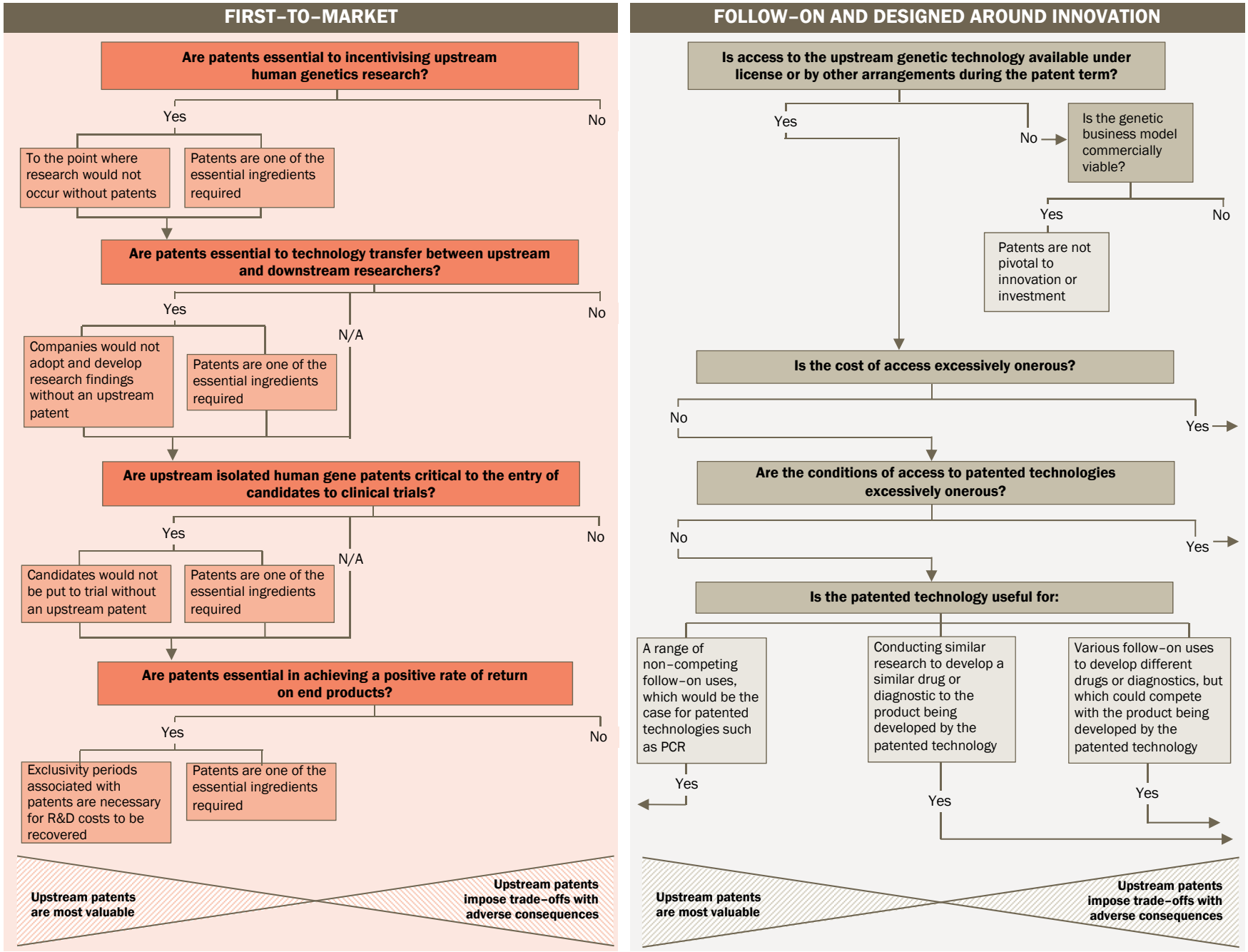
This report has drawn together various data sources and highlighted many of the key benefits and costs of patenting in order to:

- provide an order of magnitude around the known and tangible economic impacts of isolated human gene patents; and
- identify areas where costs, risks or uncertainties are likely to highlight the trade-offs of the patent system in the context of isolated human gene patents.

There are so many permutations of possible outcomes that it is too simplistic, and indeed fraught with danger, to attribute all costs or all benefits to upstream isolated human gene patents.

Rather, this analysis leads to a series of threshold questions that can help to illuminate when isolated human gene patenting is likely to be most valuable, and when it is likely to impose more adverse consequences (chart 5.14).

5.14 Threshold questions in assessing the economic impact of isolated human gene patents



Source: The CIE

These threshold questions are not exhaustive or definitive, with different questions relating to first-to-market inventions as well as follow-on or designed around innovation. For instance:

- To what extent are patents essential to incentivising upstream human genetics research?
- To what extent are patents essential to technology transfer between upstream and downstream researchers?
- Are upstream isolated human gene patents critical to the entry of candidates to clinical trials?
- To what extent are upstream patents critical in achieving a positive rate of return on R&D?
- Is access to upstream human genetic technology available under licence or by other arrangements during the patent term?
- Is the cost of access to patented technologies excessively onerous?
- Are the conditions of access to patented technologies excessively onerous?
- What is the patented technology useful for? Costs are likely to be less significant when research relates to the development similar products, compared to follow-on uses to develop different but competing products, or useful for developing non-competing follow-on uses.

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PART 1

Appendices

A Patent Search Methodology

To determine the total number of isolated human gene patents in Australia, a full text search was undertaken of the claim set of all AusPat records — an online repository of granted patents and patent applications in Australia —using keyword search terms 'SEQ' or 'sequence' in conjunction with International Patent Classification (IPC) marks — see box A.1.

Two separate searches were undertaken to identify relevant patents for this study. The first was performed on the 9 November 2012 using the terms and IPC marks outlined in box A.1.

Initially, the search was undertaken by applying the search criteria to the Auspat database. Subsequent analysis of AusPat and its manual found that prior to 1 April 2004 Auspat published all PCT applications filed with WIPO, while after that date it records the PCT applications that eventually enter the national phase in Australia. Auspat is case-sensitive, and there were differences in the samples when capital letters were added to the front of words, while plurals are not automatically included in singular expressions, so a search for 'sequence' would not extract the plural 'sequences' or the capitalised 'Sequence'.

This created uncertainty with respect to whether the sample was representative, as there were in excess of 100 000 PCT filings at WIPO, but only 15 830 of those actually entered the national phase in Australia. So the sample was biased. There were also issues around the plurals and capitalisation as observations had been missed from the initial searches.

A subsequent search was performed on the 20th of March 2013 to confirm that applications were applied through the domestic route or were PCT filings that eventually had national phase entry. The patents randomly selected from the first search strategy were deemed to be appropriate for the purpose of estimating the total number of isolated human gene patents filed in Australia. Having learnt more about the distributions of the granted Australian patents, the March 2013 search took a broader approach and included 'DNA' as a key word, while broadening the potential categories where isolated human gene patents might have been classified as we had observed outliers.

Analysis on who holds granted isolated human gene patents used a combination of granted patents from both the November 2012 search and the March 2013 search. Using only the grants we are confident that the patents were filed in Australia and were granted here. There are slight concerns that the pre-2004 data may be understated, as a proportion of those applications from the November search would be PCTs that could not have been granted in Australia. Because this would understate the number of grants filed before 2004, the results which show that the vast majority of isolated human gene patents granted were filed before 2003, highlighting that filings and grants in this area

declined after 2003. The grant data was also combined to increase sample size and provide an accurate profile of granted patenting activity in Australia."

The results of the second search strategy were used for the extrapolation of the random sampling results to total patent activity (including for total patents that were ever granted as well as total patents currently in force in Australia). The patents randomly selected from the first search strategy were combined with the patents randomly selected from the second search strategy to increase sample size and provide an accurate profile of patenting activity in Australia.[193]

A.1 International Patent Classification Mark

The IPC is an indexing system based on the technology of the patents established by the Strasbourg Agreement 1971 and maintained by the World Intellectual Property Organization (WIPO). More than one IPC mark can be allocated to an invention. There is no discrete IPC mark for isolated *human* genes, i.e. the IPC system does not distinguish isolated human gene sequences from gene sequences isolated from other mammals.[194]

There were four main IPC sub-classes chosen, one being the C12N15, which consists of inventions within mutation or genetic engineering. Specifically the C12N15/12 to C12N15/28 subclasses were chosen as they described 'genes that encoded animal proteins'. IPC marks in the C07K group are for technologies that use peptides (proteins) and may be for pharmaceutical or other uses. The November 2012 search also searched the C12Q group (technologies relating to proteins) and the March 2013 search also searched for the C07H group (technologies including nucleotides and nucleic acids).

Both the November 2012 and March 2013 searches employed multiple search strategies, as set out below.

Search strategy, November 2012

Three separate searches were performed on the 9 November 2012 using the search terms 'SEQ' or 'sequence' and IPC marks as these terms will be in any patent claiming a genetic or protein sequence.

- Search 1 was a full text search of the claim set for all AusPat records using keyword search terms 'SEQ' or 'sequence' and a search within that data set for at least one IPC mark in the C12N 15/12 to C12N 15/28 range, which identified 4456 records.
- Search 2 was a full text search of the claim set for all AusPat records using keyword search terms 'SEQ' or 'sequence' and a search within that data set for at least one IPC

193 The search strategy was designed by IP Australia. IP Australia was responsible for reviewing and classifying patents. The CIE performed statistical analysis on the information provided by IP Australia and developed the analysis for this report.

194 IP Australia/DIISR submission to the Senate Gene Patents Inquiry at paragraphs 7.1 to 7.11, and Appendices C and D

mark in the CO7K sub class, but not C12N15/12 to C12N15/28 mark, which identified 1375 records.

- Search 3 covered full text search of the claim set for all AusPat records using keyword search terms 'SEQ' or 'sequence' and a search within that data set for at least one IPC mark in the C12Q 1/68 (but without any C12N15/*, CO7K7/* or CO7K4/12) which identified 1963 records.

The records from each the searches were pooled, and duplicates were removed. From this list, patents with an A01H mark were also removed, which are patents that describe genetically modified *plant* technology, but due to the broad search strategy had been inadvertently captured.

The result was a list of 7649 unique AusPat records, from which 983 patents were randomly selected for close review.

From the random sample of classified isolated human gene patents, the number of granted patents was 165, including those that are in force, and those that are no longer in force.

The descriptors recorded for these patents included those over the claims, as well as applicant details such as country of origin, public or private applicants and earliest priority date.

Search Strategy, March 2013

The March 2013 search included only those applications from 1980 onwards that were applied through the Paris Convention (domestic route) or those for which Patent Cooperation Treaty (PCT) filings eventually had national phase entry.

The search strategies were employed to capture all isolated human gene sequence patents and applications in Australia. This included the use of IPC marks in conjunction with search terms, or using search terms only. The search terms used were all varieties of the word 'sequence' and all varieties of the key-words 'DNA', 'nucleic', polynucleotide' and 'nucleotide'.

- Search 1 covered all filings from IPC subclasses C12N15/12-28, including any variety of the word 'sequence'. This search identified 4 266 records.
- Search 2 covered all filings to all IPC classes of the CO7H and CO7K group, that include all varieties of the word 'sequence' and all key-words 'DNA, nucleic, polynucleotide, and nucleotide'. It excluded applications from Search 1. This search returned 21 112 records.
- Search 3 included all filings with the search terms of all varieties of the word 'sequence' and all key words 'DNA, nucleic, polynucleotide, and nucleotide'. It excluded any applications found in Search 1 and Search 2. This search returned 28 928 records.

The result was a list of 54 306 unique AusPat records, from which 1 210 patents were randomly selected for close review.

From the random sample of classified isolated human gene patents, the number of granted patents was 151, including those that are in force, and those that are no longer in force. Of these, 122 were from search strategy 1.

Due to the manual nature of isolated human gene patent categorisation, more descriptors were recorded from the November 2012 sampling compared to the March 2013, as the latter search was designed specifically to robustly estimate total patent numbers, rather than record comprehensive information on sampled patents.

The sampling methods from the March 2013 search strategy only included patents from 1980 onwards (to account for differences in PCT filings) and was used to extrapolate the total number of isolated human gene patents in Australia and the number of these that are still in force.

To increase the sample size and improve its accuracy, the analysis of the sample of random patents developed in Chapter 3 of this report includes the 165 granted patents from the November 2012 search and 105 (minus 17 duplicates from the November 2012 search) granted patents from the March 2013 search.[195]

Excluded patent results

During the randomised sampling of the patent list, many patents were identified as not fitting the description of an isolated human gene patent. This was because the search criteria used the IPC Mark of C12N and C07K, which does NOT distinguish between human and non-human patents. Further, more than one IPC mark can be applied to a patent and the IPC marks are quite broad – the search term 'sequence' can also be found in any genetic engineering patent and not only those relating to a specific gene.

195 The November 2012 search did not randomly select patents from each search strategy, whereas the March 2013 did, when it was particularly important to weight the sampling results to the population size for each search type. To ensure consistency in the random selection of patents across the November 2012 and March 2013 searches, only patents from search 1 in March 2013 were combined with the November 2012 sample as only one search bucket could be used and this bucket contained the most (81 per cent) of patents.

Examples of excluded patents are as follows.

- Microbial, viral, plant and non-human animal gene patents, for example, AU 2011201207: 'Genemarker for evaluating genetic potential for marbling in bovine individual and method for evaluating genetic potential for marbling using the same'. This invention described a marker for marbling in cows.
- Patents that did not claim a specific gene sequence, but actually described processes of novel genetic engineering technology. For example, AU 2010274809: 'A method of removing nucleic acid contamination in reverse transcription and amplification reactions'. This invention described the removal of contaminants in a process used in the laboratory.

B Guidelines for the licensing of genetic inventions

The OECD have developed a set of Guidelines that apply to the licensing of intellectual property rights related to genetic inventions used for human health care. The guidelines encourage 'a balanced intellectual property system' where the development and dissemination of knowledge and innovations with a view to fostering scientific, technical and social progress is balanced with the patentee's right to exploit or commercialise such innovations in a manner which promotes access to innovations and a return on investment. Selected OECD best practice guidelines for the licensing of genetic inventions are provided in table C.1.

B.1 Selected OECD best practices for the licensing of genetic inventions

General principals
1.1 License agreements should permit licensees to develop and further improve the licensed genetic inventions.
1.4 Confidentiality provisions should permit the dissemination of information while taking into account the need to protect undisclosed information and capitalise inventions in the marketplace.
1.5 License agreements should not systematically provide the licensor with exclusive control over human genetic information derived from individuals through use of the licensed invention.
1.6 Rights holders should seek the full exploitation of their genetic inventions.
1.7 License agreements should address the rights of the parties to use the improvements to the licensed genetic invention following termination of the agreement.
Health care and genetic inventions
2.1 Patent holders should license genetic inventions for research, investigation and clinical diagnostic purposes broadly.
2.2 Licensing practices should permit national or local providers to use genetic inventions in order to provide health care services.
2.3 License agreements should not restrict access by the licensee to databases generated from licensed genetic inventions in their efforts to develop new therapies, products or services.
2.4 License agreements should permit licensees (e.g. health care providers) to offer patients flexibility and choice with respect to the type and nature of health care products and services.
2.6 Public and private sector agents should develop mechanisms to assist the use of genetic inventions to address unmet and urgent health needs in developing and developed countries.
Commercial development
4.1 Should several licenses be required, license agreements should include a mechanism to set a reasonable overall royalty burden for genetic invention products and services.
4.2 License agreements should include terms that maintain low barriers for access to genetic inventions. For instance, this may mean such agreements do not include excessive up-front fees.
4.3 License agreements should avoid reach-through rights, so as to foster broad and unencumbered access to research tools.
4.4 Private and public sector participants should collaboratively develop mechanisms to decrease transaction costs in acquiring rights to use technology
Competition
5.1 License agreements should avoid unduly restrictive tied-selling.
5.2 License agreements should avoid non-compete clauses in areas beyond the scope of licensed genetic invention.
5.3 License agreements relating to foundational genetic inventions should generally be non-exclusive to encourage broad access for patients and use of the genetic invention.

Source: OECD 2005, Draft Guidelines for the Licensing of Genetic Inventions, February.

C Patents of genetic tests

C.1 Genetic tests listed on the Medicare Benefits Schedule and their patents

Disease	Gene	MBS	Patents (US)	Patent(AU)	Status of AU patent or application
Thrombophilia	FVL (F5)	73308	5874256	690644	Granted (Expiry 14-02-2015)
Haemochromatosis DNA studies	HFE (C2827 mutation)	73317	7026116, 5705343, 5712098, 5753438	733459, 722885	Granted (Expiry 04-04-2017), Granted (Expiry -08-05-2016)
Von Hippel-Lindau syndrome	VHL	73333	5654138, 5759790	1994068337, 199725931	Ceased, Lapsed
Charcot-Marie-Tooth Neuopathy Typ1 1A- Mutation Testing -Genotyping	PMP22	73294	5599920, 5780223	19922265	Lapsed
Fragile X mental retardation 1 screening – Genotyping	FMR1	73300	5658764, 6200747, 6107025, 55691144	N/A	N/A
Gene Rearrangements-APML-Genotyping	APML t(15:17)	73314	N/A	N/A	N/A
Detection of HLA-B27 (autoimmune disorders)	HLA-B27	73320	N/A	N/A	N/A
Detection of HLAB5701 prior to initiation of Abacavir therapy	HLAB5701	73323	N/A	N/A	N/A
JAK2 Mutation Analysis-Genotyping for V617F mutation	JAK2	73325	N/A	N/A	N/A
Gene Rearrangements-FIP1L1-PDGFRA-Genotyping	FIP1L1-PDGFRA	73326	N/A	N/A	N/A
Pharmacogenetics: Thiopurine S-methyltransferase	TPMT	73327	N/A	N/A	N/A
EGFR Mutations test	EGFR	73328	N/A	N/A	N/A
KRAS Mutations Testing	KRAS	73330	N/A	N/A	N/A
HER2 ISH test for trastuzumab therapy	HER2	73332	N/A	N/A	N/A

Source: The CIE

C.2 Genetic tests not listed on the Medicare Benefits Schedule and their patents

Test	Gene	Patent (US)	Patent (AU)	Status of AU patent or application
Hereditary Spastic Paraplegia - Genotyping	ATLASTIN (SPG3A or ALT1)	7649088, 7108975, 7582425	2002330025	Lapsed
BRCA1- Genotyping	BRCA1	5753441	686004, 691958	Granted (Expiry 11-08-2015), Granted (Expiry 11-08-2015)
BRCA2-Genotyping	BRCA2	6051379	773601	Granted (Expiry 30-09-2013)
Long QT-Genotyping	LQT7 (KCNJ2)	7306911	2002258922	Lapsed
Parkinsons Disease	LRRK2	7544786	2005319787	Granted (19-12-2025)
Huntington Disease	HTT	4666828	676001, 673575	Ceased, Ceased
Cystic Fibrosis (31 mutations) - Genotyping	CFTR	6730777	647408	Expired
Duchenne/Becker Muscular Dystrophy	DMD	5541074	633249, 200073786	Ceased, Lapsed
Apoloprotein E- Genotyping: Whole blood	APOE	5508167, 5716828, 6027896	677614	Granted (30-09-2013)
Canavans Disease (Ashkenazi Jewish only) - Genotyping	ASPA	5679635, 7217547	199473207	Lapsed
Cystic Fibrosis -DF508 mutation only-Genotyping	DF508	6984487	647408	Expired
Freidreichs Ataxia Gene Test (Fratazin repeat expansion on Chromosome 9)	Fratazin	6150091	199720950	Lapsed
Hearing Loss	Connexin 26			N/A
Long QT-Genotyping (Mutation Screen, 6 genes)	KCNQ1, KCNH2, KCNE2, KCNE1, SCN5	(KCNQ1 '6150104, 6277978, 6342357, 6451534, 6582913, 6972176), (KCNH2 '5599673, 6207383, 7297489'), (SCN5A '6787309, 5599673'), (KCNE1 '6323026, 6432644, 7247436'), (KCNE2 '6864364')	714041, 714527, 758048, 779477, 774194, 778566	Granted (Expiry 20-12-2016), Granted (20-1202016), Ceased, Ceased, Ceased, Granted (14-04-2020)
Machado Joseph Disease (Spinocerebellar Ataxia Type 3) - Genotyping: DNA	ATNX3 (SCA3)	5840491	N/A	N/A
Tay Sachs Disease	HEXA (Hexosaminidase A)	5217865, 5475095	N/A	N/A
X-Linked mental retardation (Retts SyndromE)	MECP2	6709817, 7670773	N/A	N/A
Complete Ataxia Evaluation	DRPLA, SCA1, SCA2, SCA3, SCA5, SCA6, SCA7, SCA8, SCA10, SCA12, SCA13, SCA14, SCA17, SCA28, FXN, APTX, POLG1, SIL1, TTPA, SETX	5,741,645, 5,834,183, 5,840,491, 5,853,995, 6,150,091, 6,303,307, 6,280,938, 6,514,755, 6,524,791, 6,844,431, 6,673,535, 6,855,497, 7,118,893, 7,119,186, 7,329,487, 7,527,931, 7,585,629, 7,655,401, and 7,824,860	735756, 200226156	Ceased, Lapsed
Myotonic Dystrophy	DMPK	5955265, 977333	199335059	Lapsed

Test	Gene	Patent (US)	Patent (AU)	Status of AU patent or application
BRAF Mutation Testing	BRAF	N/A	N/A	N/A
Achondroplasia (G380R mutation)-Genotyping	FGFR3, G380R	N/A	N/A	N/A
Alveolar Rhabdomysarcoma - t(2:13) and t(1:13)- Genotyping	PAX3 (FOXO1A)	N/A	N/A	N/A
Angelman Syndrome-Methylationtesting-Genotyping	ANCR	N/A	N/A	N/A
Atypical Teratoid Rhaboid Tumour- Genotyping	ATRT (SMARCB1, INI1)	N/A	N/A	N/A
Butyrylcholinesterase-Genotyping: DNA	BCHE	N/A	N/A	N/A
Dentatorubral-Pallidoluysian Atyophy-Genotyping: DNA	ATN1(DRPLA)	N/A	N/A	N/A
Desmoplastic Small Round Cell Tumour- EWS-WTI-Genotyping	EWRS1/WTI	N/A	N/A	N/A
Drash Disease -Genotyping	WTI Drash	N/A	N/A	N/A
Ewings Sarcoma-t(11;22), t(21;22) - Genotyping	EWSR1	N/A	N/A	N/A
Familial Mediterranean Fever- FMF (Exon 2 and 10 mutations) - Genotyping	FMF (MEFV)	N/A	N/A	N/A
Fanconi Anaemia Carrier Screening (Ashkenazi Jewish)	FANCC	N/A	N/A	N/A
Frasier Syndrome-Genotyping	WTI	N/A	N/A	N/A
Galactosaemia (Q188R & N314D mutations) - Genotyping	GALT	N/A	N/A	N/A
Hereditary Spastic Paraplegia (NIPA1 Gene) - Genotyping	NIPA1	N/A	N/A	N/A
Hereditary Spastic Paraplegia (REEP1 Gene) - Mutations Testing: DNA	REEP1	N/A	N/A	N/A
Hypochondroplasia (N540K mutation) - Genotyping	FGFR3, N540K	N/A	N/A	N/A
Long Chain-3-Hydroxyacyl Coa Dehydrogenase (LCHAD)	LCHAD	N/A	N/A	N/A

Source: The CIE.

D Patent application fees

To apply for an isolated human gene patent, initially a standard complete patent application fee of $370 and a patent examination fee of $490 are required.

A patent holder must then pay the prescribed maintenance fees to keep a patent in force. Maintenance fees for standard patents commence on the fourth anniversary ($300 payable) and extend incrementally up to the 19th anniversary ($1120 payable) of the filing date (or up to the 24th anniversary ($2300 payable) for pharmaceutical patents that have had their term extended).[196] A standard patent will cease if the prescribed fees are not paid.

D.1 Selected patent fees, 2013

Type of patent fee	Cost ($)
New application	
Provisional Patent Application	110
Standard Complete Patent Application	370
Patent National Phase Entry Application	370
Examination/acceptance	
Patent Examination Fee	490
Filing a request for re-examination	800
Request for International Type Search	2 200
Standard Complete Patent - Acceptance	250
Standard Patent Renewals	
Renewal Payment Late Fee	100 for each month, or part thereof
Standard Patent - 4th Anniversary	300
Standard Patent - 10th Anniversary	500
Standard Patent - 15th Anniversary	1 120
Standard Patent Pharmaceutical - 20th Anniversary	2 300
Extension of Time Fees	
Request for Extension of time.[a]	100
Opposition fees	
File an opposition to an application or objection to an action	600
Extension of time to serve evidence	500 for each month or part thereof
Request for determination of a dispute between applicants	600

(Continued on next page)

196 These fees refer to payment by eServices, however when renewing a Standard Patent by other means (for example by mail, fax or at an IP Lodgement counter) a higher fee will apply. See IP Australia, Patents — Fees, available at http://www.ipaustralia.gov.au/get-the-right-ip/patents/time-and-costs/fees/.

Type of patent fee	Cost ($)
Opposition fees	
Filing a request for dismissal of opposition	600
Filing a request for a Hearing	600
Appearing at Hearing	1 000

[a] Fee applicable where circumstances are beyond the control of the person concerned.

Note: This is a selected list of fees payable to obtain and maintain a patent. For a comprehensive fee schedule see *Patents Regulations 1991*, Schedule 7, Fees.

Source: IP Australia and the CIE.

E Patent profile and descriptors

E.1 Patent profile and descriptors

Classification	Descriptors
Key elements	
Number	Application Number
Date	Filing Date, Earliest Priority
International Patent Classification Mark	First IPC Mark
Status	Application Status: Granted patent: Granted, Expired, Ceased, Revoked
Title	Title
Applicant	Applicant(s), Inventors(s), Country of Origin of Applicant(s), Public (University/Medical Research Institute/Hospital) vs. Private (Biotechnology, Pharmaceutical or Diagnostic company)
Claim type	
Gene	Full-length isolated gene sequence encoding a protein vs. Portion of the gene for use as a probe or primer) vs. Method of use for isolated gene sequence only
Counterpart in nature	Counterpart in nature (gDNA claimed and exemplified or gDNA claimed but not exemplified) vs. No counterpart in nature (cDNA sequence or partial only)
Method	Diagnosis (use of the gene or protein sequence to diagnose or prognose disease or disorders associated with the gene (diagnostic kit/assay/probe) 1 Therapeutic (treatment): a) therapeutic to treat a disease or disorder associated 2 Therapeutic (treatment): a) therapeutic to treat a disease or disorder associated with the gene (protein or with gene therapy); and b) methods of identifying molecules that modulate or interact with the gene wherein the methods are directly based on the use of the sequence.

Data source: The CIE.

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