Clinical implications of genomics for cancer risk genetics

David M Thomas, Paul A James, Mandy L Ballinger

The study of human genetics has provided substantial insight into cancer biology. With an increase in sequencing capacity and a reduction in sequencing costs, genomics will probably transform clinical cancer genetics. A heritable basis for many cancers is accepted, but so far less than half the genetic drivers have been identified. Genomics will increasingly be applied to populations irrespective of family history, which will change the framework of phenotype-directed genetic testing. Panel testing and whole genome sequencing will identify novel, polygenic, and de-novo determinants of cancer risk, often with lower penetrance, which will challenge present binary clinical classification systems and management algorithms. In the future, genotype-stratified public screening and prevention programmes could form part of tailored population risk management. The integration of research with clinical practice will result in so-called discovery cohorts that will help identify clinically significant genetic variation.

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The Kinghorn Cancer Centre and Cancer Division, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia (Prof D M Thomas FRACP); **Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia** (Prof D M Thomas, P A James FRACP, M L Ballinger PhD); **and Research Division** (Prof D M Thomas, M L Ballinger) **and Familial Cancer Centre** (P A James), **Peter MacCallum Cancer Centre, Melbourne, VIC, Australia**

Correspondence to:
Prof David M Thomas, The Kinghorn Cancer Centre and Cancer Division, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia
d.thomas@garvan.org.au

Introduction

Conceivably, more has been learnt about the biology of cancer from the study of human genetics than from any other discipline. Development of the field of human genetics has shaped the way inherited cancer risk is viewed. For more than 100 years, cancer has been known to run in some families.[1,2] The clinical and biological significance of several major tumour suppressor genes—eg, *TP53, RB1, BRCA1, BRCA2,* and *APC*—was identified through the study of families showing heritable patterns of cancer. Between 1980 and 2000, much progress was made in isolating regions of the human genome that are associated with increased cancer risk. The integration of germline genetics with subsequent somatic evolution is exemplified by the so-called Vogelgram, which postulates a distinct order of events that contribute to the evolution of at least some types of colorectal cancer.[3] Additionally, the link between familial polyposis and bowel cancer in familial adenomatous polyposis[4] was fundamental to assigning a causal role for *APC* in this disease.[5,6] Furthermore, segregation within large pedigrees with early onset cancers, together with reverse mouse genetics, provided evidence for the pathogenetic role of tumour suppressor genes. Cell and molecular biologists subsequently defined key pathways and processes fundamental to the present clinical concepts of cancer.[7,8]

The development of clinical cancer genetics has been driven by the number of families with higher than average cancer risk and the accumulating evidence for the effectiveness of cancer screening and prevention strategies. Familial cancer management has been most successful in the organ-specific, single-gene breast and bowel cancer syndromes because of the presence of effective screening strategies and the option to surgically remove the tumour at a curable stage in both disorders. These aspects contribute to the continued predominance of breast and bowel cancer in familial cancer clinics, in which predisposition to these cancer types is present in more than 80% of attending families.[9] Alternatively, the clinical management of Li-Fraumeni syndrome—in which carriers of germline mutations in *TP53* are prone to an extremely high risk of cancers in several anatomical sites—has progressed much more slowly, despite the fact that the causal gene was identified before *BRCA1, BRCA2,* or *APC*.

Clinical cancer genetics is founded on a heritable cancer model that is characterised by Mendelian patterns of cancer inheritance within families. This Personal View explores the implications of recent developments in genomic technologies for the clinical cancer genetics specialty.

Genomics

Two elements are fundamental to the transformative power of genomic technologies in cancer genetics. First, the capacity to derive an increasingly comprehensive, if not absolute, understanding of the genetic alterations within cancers, which before genomic technology was restricted to a handful of genes. The genetic makeup of cancers revealed by genomic technology is astonishingly complex, with some tumours carrying thousands of genetic changes. Currently, a major challenge is to distinguish between so-called driver and passenger mutations, which is crucial to the exploitation of this information for therapeutic puposes.[10] The dynamic field of somatic cancer genetics and its implications for cancer care is beyond the scope of this Personal View. Here, we focus on germline determinants of cancer risk. The second key element is the need to reduce sequencing costs. The cost of sequencing the first whole human genome was about US$3 billion, and took more than a decade to complete.[11] Subsequently, sequencing costs have fallen exponentially to $1000 per whole human genome,[11] and can be generated (if not analysed) in less than a week. Genomics can be used to comprehensively catalogue the genetic landscape of cancer predisposition and the reductions in cost and improved throughputs have meant that genomics is accessible to the broader community affected by cancer.

The architecture of genetic risk

The overall genetic contribution to cancer risk can be best estimated from studies of cancer incidence in monozygotic and dizygotic twins.[12] In a landmark study of almost 45 000 twins, accurate estimates of the genetic and environmental basis for cancer were generated for several

different cancer types.[12] Genetic causes of cervical and lung cancers are negligible, whereas 27% of breast cancers and 42% of prostate cancers can be explained by genetic factors. Enormous efforts have been made to identify the genes that contribute to the heritable component of cancer. A small proportion of the genetic risk for breast cancer, for instance, is explained by the rare and highly penetrant variations in *BRCA1, BRCA2*, and *TP53*, which probably account for less than 10% of the genetic basis for breast cancer.[13–15] These data have come from linkage-based pedigree studies of families that have a higher than average incidence of cancer. Pedigree-based methods have also been used to study very rare, high-penetrance genes, such as *PALB2*,[16] and more common variants in genes with moderate penetrance, such as *CHEK21100delC* and specific *ATM* variants,[17,18] that further explain an additional proportion of genetic risk. By contrast, genome-wide association studies (GWAS) have identified common genetic variants with low penetrance associated with heritable breast cancer risk in the general population. Currently, 67 of these low penetrance breast cancer variants have been identified and these account for 28% of familial breast cancer risk.[19,20] GWAS use arrays of single nucleotide polymorphisms (SNPs), which are known to be present at greater than 5% frequency in the general population, to identify loci that segregate with increased cancer risk. Some cancer-associated genomic regions seem to be gene deserts, which challenges the gene-centric models in cancer biology. Large multinational consortia, such as the Breast Cancer Association Consortium, have analysed over 100 000 cases and controls, which are needed to detect rare, low penetrance variants. Collectively, research on the individual contribution from rare, high-penetrance variants to common, low-penetrance variants in breast, ovarian, and prostate cancers has identified substantially less than half of the genetic basis for these diseases.[20–22]

The so-called missing heritability

A comprehensive understanding of the genetic basis of cancer remains a challenge. Efforts to map genetic risk have focused on a small subset of cancers, and research into less well studied cancer types is needed. Breast and bowel cancers account for more than 80% of the daily caseload in Australian familial cancer clinics, but only 25% of all cancers, and 16% of total cancer deaths.[23] Moreover, as the genetic circuitry varies substantially between cancer types what is understood from breast, ovarian, and bowel cancers may not be relevant for other cancers.

Even in intensively studied cancers, missing heritability is an unresolved issue. Until recently, research methods were not affordably sensitive or specific, or cost-effective to detect smaller effect sizes or rarer variants on a population-wide scale with either family-based or case-control methods. Missing heritability is partly due to unidentified rare variants, typically with moderate or high penetrance. Whole genome sequencing on a large scale could be used to identify many more novel rare variants of this kind, especially in understudied cancer types. Furthermore, implications of polygenic effects on cancer risk can be assessed by assaying multiple genes simultaneously, either by targeted panels or by whole genome sequencing. Results from these assays suggest that some individuals might carry many potentially important variants in more than one gene,[24] and the combined effects of common, low-penetrance loci identified in GWAS might account for a substantial proportion of breast cancer risk in high-risk families.[25] Genetic interactions in distinct moderate-penetrance genes also probably account for some of the variation in cancer risk at the population level. These genetic interactions are assumed to be additive, and epistasis will account for individual cancer susceptibility, such that the magnitude of the total risk is more than the sum of the contribution of each individual allele.

From the gene to the variant

Clinical interpretation of genetic variation is influenced by Mendelian principles. Pathogenicity assigned to individual variants in genes assumes a binary form: they are either pathogenic and responsible for the phenotype associated with the gene or they are classified as neutral or variants of uncertain significance and deemed clinically irrelevant. Historically, the terms low, medium, and high penetrance have been used at the gene level, on the assumption that all pathogenic variants within those genes have the same effect. However, variants within any given gene will probably span the full range of activity, from complete loss-of-function or dominant negative effects, to more moderate effects and complete neutrality. Some variants might also result in a gain-of-function, even in tumour suppressor genes, which could result in germline genetic variation that, in theory, could protect against cancer. In a small number of specific cases, variation on a restricted scale has proved tractable to classification. The American Thyroid Association classification of the activating mutations in the *RET* proto-oncogene,[26] responsible for penetrance of medullary thyroid cancer, which ranges from almost 100% penetrance in early infancy to reduced penetrance of adult onset disease, is one example. Reduced or altered penetrance alleles have also been recognised in some of the best-known high penetrance cancer genes, including *BRCA1* (R1699Q)[27] and *TP53* (R337H).[28,29]

A continuous range of biological variation is not compatible with an artificial, binary classification of cancer risk. Classification systems such as those proposed by the American College of Medical Genetics (ACMG)[30] or the International Agency for Research on Cancer (IARC)[31] use data for the biological effects of the variants to predict the clinical significance of genetic variants (table). A variant might be of uncertain clinical significance because the biological effect is not known, even if that clinical effect is major; alternatively, the variant might be of uncertain clinical significance because substantial evidence suggests that the biological effect is moderate and insufficient to

justify clinical intervention (figure). Many of the alleles soon to be identified by genomic techniques will fall into a category in which alleles with moderate effect are indistinguishable from those with insufficient evidence for classification.Concurrently, the parallel testing of multiple genes using genomics will place further stress on a classification system that evolved to describe risk as the presence or absence of the effect of one major gene. An individual's cancer risk is thought to be the sum (or a more complex function) of the contributions from each allele, and this seems to hold true when moderate-risk alleles are included, or when the modification of known high-penetrance genes is considered. Accordingly, an individual with one fully penetrant mutation in *TP53*, which is the present focus of cancer genetic services, might carry the same high and actionable risk for the development of cancer as an individual who carries two partially penetrant but complementary variants of uncertain significance. The cumulative effect on an individual's genetic risk of cancer will be the quantitative product of three substituent parts: the maximum possible contribution of any given gene, the specific effect within that range for a given variant, and the sum of all such alleles carried by the individual concerned.

Clinical implications

Despite substantial improvements in genomic technology, data are still insufficient to determine an individual's genetic risk of cancer and to apply this risk in the clinic. Translating this knowledge into the clinic is challenging. Genomic techniques are increasingly being applied to cancer populations, driven in part by public demand for therapeutic interventions based on genetic targets. Furthermore, reduction in the cost of genetic testing will lead to clinical germline testing. The economic argument for the restriction of testing is diminishing as regions of the genome that contain variants of clinical significance continue to expand. Germline determinants of cancer risk will be identified increasingly in individuals who do not have a family history of cancer, which was exemplified by a recent report of germline mutations in patients with apparently sporadic pancreatic cancer that showed that fewer than half of the carriers of cancer-causing mutations had a family history of cancer.[34]

Interpretation of genetic variation will be extrapolated from the dominant Mendelian familial cancer setting. However, the penetrance estimates based on family history usually overstate the actual contribution of that variant to individual cancer risk when ascertained in a population setting, as exemplified by *BRCA1* mutations.[35] Overstatement of the actual contribution of a variant to cancer risk could be a result of undefined modifier genes that enhance the phenotypic expression of the variant in cancer-prone families, but that are typically absent in the general population. However, the presence of a variant in an affected individual with an absence of a family history does not automatically imply that a variant is not highly penetrant. Population sampling will provide a better estimate of de-novo mutation rates. Family history is not a reliable guide to the penetrance of de-novo variants. In addition, the frequency of de-novo mutations varies widely from gene to gene. *TP53* de-novo mutations have been predicted to be present in 30% of sarcoma cases,[36] whereas de-novo mutations of *BRCA1* and *BRCA2* are rare.[37] Clinically, de-novo variants have fewer implications for ancestors of the proband than for their progeny. Clinical implications of polygenic interactions are even less well understood, but could be substantial.

Clinical recognition of increased genetic risk will shift from family history to personal markers, such as the age of cancer onset, the range of cancers considered, and the presence of multiple primary cancers in one indivdual. About 2·5% of cancer cases occur in people younger than 30 years. Many cancers that occur in this age group, such

	IARC class[33]	Probability*	Clinical action
1: Variant reported and recognised as a cause of the disorder	5: Pathogenic mutation	>0·99	Tailored surveillance and reproductive options for mutation carriers; predictive genetic testing available to family members
2: Unreported variant of a type expected to cause the disorder	4: Probably pathogenic	0·95–0·99	Tailored surveillance and reproductive options for mutation carriers; predictive genetic testing available to family members
3: Unreported variant of a type that might or might not cause the disorder	3: Variant of uncertain significance	0·05–0·95	Surveillance can be recommended on the basis of clinical scenario; predictive testing of family members not available
4: Unreported variant that is probably not the cause of the disorder	2: Unlikely to be pathogenic	0·01–0·05	Not clinically actionable
5: Variant reported and recognised as neutral	1: Neutral variants	<0·01	Not clinically actionable
6†: Variants that are not causative but have been associated with the disorder	(Mostly classified as class 1 or 2)	NA	Limited clinical interpretation in isolation

ACMG=American College of Medical Genetics. IARC=International Agency for Research on Cancer. NA=not applicable. *Probability that the variant is pathogenic based on the summation of available evidence. †This category includes common variants from genome-wide association studies that are not classified (or would be considered neutral) in the IARC classification.

Table: **Sequence variant classification systems according to ACMG category[32]**

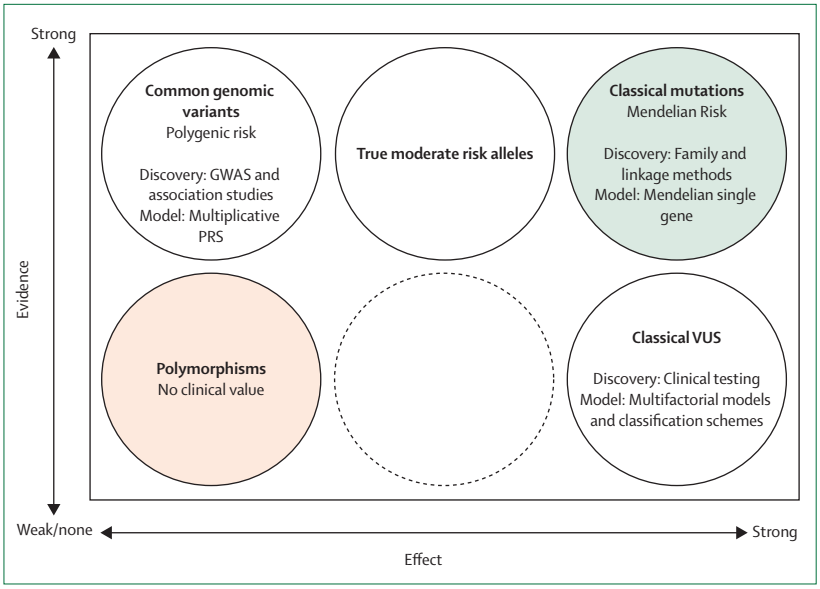

***Figure*: Classification of variants on the basis of both the size of their effect on cancer risk and the strength of the evidence**

For both size effect and strength of evidence, a gap exists in the present approach to moderate risk variants (as indicated by the circle with the dotted line). GWAS=genome-wide association studies. PRS=polygenic risk score. VUS=variant of unknown significance.

as Ewing's sarcoma, are not typically associated with familial cancer syndromes. Affected individuals might therefore be enriched for polygenic cancer risk, which accounts for early onset and absence of familial patterns. People younger than 30 years are also more likely to be cured than patients older than 30 years, with more than 80% of individuals surviving their cancer diagnosis. Despite the historical fatalism attached to a diagnosis of Li-Fraumeni syndrome, the presence of a germline mutation in *TP53* does not imply incurability,[36] and evidence is accumulating as to the benefits of screening for this cancer syndrome.[32,33] Finally, unrecognised de-novo or polygenic cancer risk might confer an increased risk of second malignancies, particularly because of exposure to carcinogenic therapies.

Genotype-first cancer risk assessment has the potential to extend the benefits of personalised risk management developed in the single-gene era to the general population. Although debated, substantial evidence supports population-level mammographic and bowel cancer screening.[38–40] Stratification of risk on the basis of genetic information could enhance the cost-effectiveness of such programmes. As newer, more sensitive and less organ-specific screening technologies become available, such as whole body MRI, the opportunities for intervention could extend beyond organ-specific cancer predisposition syndromes.[41,42] Preventive strategies, such as chemo-prevention, prophylactic surgical mastectomy, and lifestyle modifications such as not smoking, might also be more effective when tailored to high-risk populations.[43] Recent data suggest that chemoprevention might benefit high-risk familial breast cancer and high-risk familial bowel cancer populations, which might extend to populations in which risk has been identified by genotype.[44–49]

From a public health perspective, genomics could be used to improve cancer outcomes, but at what cost? More efficient and effective investment in public health strategies could offset some of the costs. The distribution of genetic cancer risk in the general population follows a roughly Gaussian distribution.[50] Genomic screening will therefore identify people at increased risk of cancer and those who carry a lower than average cancer risk. For individuals with a lower than average cancer risk, their risk might be so low that participation in public screening programmes—eg, universal mammographic screening over 50 years of age—is not cost effective. Therefore, excluding these individuals from these screening programmes could save funds that could be invested in treating high-risk populations. However, whether a change in screening policy would be regarded as acceptable by low-risk individuals or at a societal level is not clear.[51] Moreover, it is as yet unclear whether the costs of genomic testing the total population to identify those at lowest risk would offset the savings in cancer screens avoided.

Many of these aforementioned policy decisions are for future consideration. From a more immediate and practical perspective, clinicians should be mindful of the importance of taking a family history, and whether or not a referral for clinical genetic counselling should be considered. Although family history will probably be only one of several factors considered in the future, it remains an important predictor of the genetic contribution to cancer risk. Improved integration of clinical geneticists into tumour-specific multidisciplinary care, outside of breast and bowel cancers, would also be beneficial. Although far from standard of care, genetic testing will move increasingly to panels of genes rather than single-gene tests, both for cost reasons and efficiency of detection of causal mutations.

Implications for cancer risk genetics research

The inevitable identification of clinically-relevant pathogenic variation, both expected and incidental, presents an interesting problem for research into cancer genetics. Some studies have recruited participants on the basis that no findings of any kind would be returned to them. However, genetic information identified in the course of research could be important, even critical, to the health of participants. Moreover, if we aim to translate the knowledge generated from genetic research into human health outcomes, discovery research will inevitably be associated with interventions. This raises the problem of informed consent. Meaningful informed consent for research into a single gene is challenging, let alone for the panel of 56 genes that the ACMG considers clinically actionable.[52] At the whole genome level informed consent is impossible, partly because of the number of genes to be considered. This problem is compounded because people react differently to an

abstract proposition about gene testing, compared with their response in practice.[53] Although 50% of people might theoretically consider genetic testing for a high-penetrance gene such as *BRCA1* or *BRCA2*, in practice the uptake is much lower.[54] Similar data for Huntington's disease gene testing reinforce the impression that theoretical consent might not be representative of decision making in practice.[55] Consent for return of results in a research context is necessarily abstract, because future consequences can ony be imagined. Furthermore, the clinical genetics specialty is advancing so rapidly that information quickly becomes outdated, and consent is no longer relevant. For example, until recently, mutations in *PALB2* were thought to have an intermediate clinical significance.[16] Because the implications of genetic testing extend beyond the index case, consent will probably always be provisional and subject to regular review. The review process will depend on continuous assessment by a multidisciplinary panel with expertise in clinical genetics, genomics, bioinformatics, genetic counselling, and ethics.

Ironically, variants of uncertain significance are balanced by variants of clear significance that need clinical management. Discovery-based genomic research will inevitably need a clinical management programme to achieve a clinical duty of care. A new challenge to understand germline determinants of cancer risk will be to bring together the extraordinarily rapidly evolving field of genomics with the inherently conservative fields of clinical research and care. Research cannot proceed without the support and engagement of the clinical genetics community, for whom the massive capacity of genomics has substantial resource and process implications. As with clinical trials, the clinical management aspects of genomic research will be best undertaken in centres with experience of clinical research, before translation into common practice.

Conclusions

Advances in the genomics field will continue to have profound effects on clinical cancer genetics. Improvements, such as cost reductions and increased capacity in genetic testing, will change the way risk is ascertained. The emphasis on strictly selecting a specific gene test on the basis of pedigree patterns will change to an increase in screening on the basis of age. Thresholds for clinical significance of variants will continue to change, because of the accelerating stream of data that supports (or refutes) pathogenicity, and parallel data on the benefits or disadvantages of interventions. Recessive and polygenic types of increased cancer risk will be identified more rapidly, which will further change concepts of genotype–phenotype correlations. The genetics of cancer risk will shift from a qualitative basis rooted in a binary classification of variation into a more nuanced and quantitative form. Operationally, mathematical, statistical, and bioinformatics expertise will be crucial to interpretation of risk. Quantitative algorithmic risk assessments used in genetic counselling for breast and bowel cancer syndromes will extend to a wider population. The routine incorporation of cancer genetics in multidisciplinary care will spread from a small range of cancer types to all cancers, and particularly those that affect the young. Finally, the iterative relation between discovery and intervention will mandate a greater integration of research with the clinic. This will parallel the integration of cancer trials into state-of-the-art cancer care, to simultaneously generate and implement the evidence base for cancer management.

Search strategy and selection criteria

We found references for this Personal View through searches of PubMed by use of the search terms "cancer", "genomic", "familial", "hereditary", "heritability", "genome-wide association study", "population", "germline", "Mendelian", "polygenic", "next generation sequencing", "massively parallel sequencing", "bowel cancer", "ovarian cancer", and "breast cancer". Only papers published in English before January, 2015, were included, and priority was given to recent publications.

Contributors
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Declaration of interests
We declare no competing interests.

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