Brief Report

Public Health Genomics

Public Health Genomics 2019;22:140–144
DOI: 10.1159/000502917

Received: March 24, 2019
Accepted: August 25, 2019
Published online: September 24, 2019

Healthcare System-Funded Preventive Genomic Screening: Challenges for Australia and Other Single-Payer Systems

Paul Lacaze[a] Jane Tiller[a] Ingrid Winship[b]

[a]Public Health Genomics, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia; [b]Department of Genomic Medicine, Royal Melbourne Hospital, Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia

Keywords
Screening · Prevention · Genetic testing · Ethics · Policy

Abstract
The prospect of healthcare systems offering population-based preventive genomic testing to all adults is becoming feasible. Some single-payer or state-funded healthcare systems are already considering offering universal testing as part of routine care. In countries with public healthcare systems, there is a unique opportunity to provide such testing in the form of a national screening program, following existing national population health-screening frameworks. This paradigm, if achievable, could help deliver a degree of testing quality and equity-of-access that may not be possible in private-payer or direct-to-consumer models, to maximize prevention and health benefits. Here, we outline some of the major challenges ahead in considering this prospect and discuss the research that is helping shape the future direction in Australia and elsewhere.

When considering the prospect of healthcare system-funded, population-based preventive genomic testing of asymptomatic adults, a variety of challenges exist. These relate to the scientific validity, acceptability, feasibility, and resourcing of such testing, as well as ethical, regulatory, and societal issues. Many of these challenges were raised following our recent cost-effectiveness analysis of offering preventive healthcare system-funded genomic screening to all young adults in Australia [1].

Here, we outline some of the major challenges related to the implementation of adult population genomic testing, including health service scalability, public education, and the ethical considerations that must be addressed as we approach this new paradigm. We discuss genomics research initiatives in Australia and elsewhere that are helping to inform future policy.

The Prospect of Population Adult Genomic Screening

Recently, a number of healthcare providers have announced plans to fund genomic testing for thousands of healthy adults [2–4]. The primary goals go beyond research, towards prevention and cost-saving for healthcare systems. Comparable pilot initiatives are also underway in the UK, Estonia, and Australia [5–7], for population genomic testing delivered through a national

E-Mail karger@karger.com
www.karger.com/phg

Paul Lacaze, PhD
Head – Public Health Genomics, Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine
Monash University, The Alfred Centre
99 Commercial Road, Melbourne VIC 3004 (Australia)
E-Mail paul.lacaze@monash.edu

healthcare system. At the prospect of population-based testing, each system faces critical decisions regarding funding and reimbursement; the provision of the attendant health services; ethical, legal, and social implications; computational infrastructure; data security; public awareness; and workforce training.

In Australia, demonstration projects for the integration of diagnostic genomic testing for routine clinical care have commenced in disease-specific research settings, such as childhood syndromes, inherited neuropathies, and inherited predisposition to colorectal cancer [8]. In addition, population-based sequencing for cancer susceptibility [9], reproductive carrier screening [7], and the diseases of ageing [10] are being investigated in research cohorts. These efforts are informing genomic health policy in Australia, guided by the recently developed National Health Genomics Policy Framework. The Australian government has also made a significant investment in a Genomics Health Futures Mission (AUD 500,000,000 over the next 10 years). These initiatives will help position Australian policy makers towards more informed decisions regarding the future approaches to population-based genomic testing and the delivery of supporting health services. However, many challenges exist.

Demonstrating Cost-Effectiveness

Before healthcare systems can consider funding population genomic screening, evidence of cost-effectiveness for the healthcare system is required. An estimated 1 in 38 adults is at-risk of a medically actionable dominant genetic condition [11] and 1 in 4 is a carrier for at least 1 recessive condition [12]. Yet most of these individuals do not know they are at an increased risk. Current targeted testing policy is estimated to miss over half the high-risk individuals in the population [13]. While it may be intuitive that combined screening for these conditions would be cost-effective, the necessary cost-effectiveness analysis of combined population screening for multiple genetic conditions required to inform health policy has been lacking.

We recently undertook a cost-effectiveness analysis of population-based genomic screening of all young adults in Australia [1]. We used a conservative model to forecast, for the first time, the combined impact of offering preventive screening for 7 different genetic conditions concurrently. We focused on dominant hereditary cancer predisposition to breast and ovarian cancer [14] and Lynch syndrome [15], modeling only highly penetrant genes; and carrier screening for 3 rare genetic conditions (cystic fibrosis, spinal muscular atrophy, and fragile X syndrome). We defined the cost-effectiveness according to an improvement in quality of life (measured in disability-adjusted life years [DALYs] prevented, an accepted and gold-standard metric [16, 17]) relative to the cost of up-front screening and subsequent medical care. We modeled cost-effectiveness from the healthcare system perspective, using a threshold of AUD 50,000/DALY prevented.

We found that, even based on this limited set of genetic conditions, population screening would be highly cost-effective, potentially saving costs for the Australian healthcare system. All conditions included in the model are currently supported by existing clinical guidelines and reimbursed health services for individuals identified to be at high risk in Australia [1]. Our study provides a platform for policy consideration, but also raises many challenges and yet-unresolved issues.

Legal, Ethical, and Social Challenges

Regardless of the potential cost-effectiveness of population genomic testing to the healthcare system, adequate legal and regulatory protections are necessary for population-level engagement with genomics. These are not necessarily in place for most countries. For example, genetic discrimination persists in Australia, especially in life insurance underwriting, where the use of genetic test results is still permitted [18]. Ongoing efforts towards policy changes continue in this area. Recently (1 July 2019), the insurance industry in Australia introduced a voluntary, partial moratorium, agreeing not to use genetic test results when underwriting policies under certain limits. However, there are still concerns regarding the lack of government oversight of this self-regulated policy in Australia, and the limits that have been chosen.

Regarding genomic data security and governance, it is currently unclear who will become the ultimate custodian of an entire nation's genetic information, should population-level testing eventuate. Direct-to-consumer companies, private and national healthcare providers, the government, and academic and military institutions are all candidates. In a culture of consumer skepticism with online data security, data governance will be paramount for gaining and maintaining public trust in genomics. As genetic databases grow, the ability to reidentify any individual within the population is increasing with precision [19], making the custodianship of genomic data a potential national security matter.

Ensuring informed consent of an entire population (or population subsets) prior to universally reimbursed testing will be a challenge. Alternatives to the current pretest genetic counseling model warrant consideration, such as group counseling, tele-counseling, chatbots, and other online methods [20]. Preserving individual autonomy for decisions around the uptake of testing and the associated interventions will be difficult in this context. Maintaining diversity of opinion and respecting the decision to "opt out" will also be challenging.

For adult monogenic cancer predisposition testing, access to testing and preventative interventions is restricted in most countries. In Australia, publicly funded gene testing is available only for individuals who meet certain criteria. Studies have shown that using family history-based criteria to determine access to genetic testing actually misses the majority of high-risk individuals in the population [13]. Out-of-pocket costs and waiting times for prophylactic surgery and access to high-risk screening vary considerably between regions as well as between public and private healthcare systems.

Population reproductive carrier screening raises other ethical challenges. Reproductive decision-making is highly personal and is influenced by legal, social, cultural, and religious mores. Reproductive carrier screening can allow high-risk couples to be informed about and prepare for having a child affected by a genetic condition. It may also facilitate early intervention and treatment to ensure the best possible health outcomes for affected children. In Australia, however, high-risk couples identified by carrier screening have limited options to avoid having affected children. Currently, the only publicly funded option (other than choosing to not conceive) is an invasive prenatal diagnosis followed by the termination of an affected pregnancy. Preimplantation genetic diagnosis (PGD) is an option to avoid severe genetic disease without termination but is not currently reimbursed by the public healthcare system in Australia. It too raises ethical dilemmas relating to IVF technology or discarding viable embryos.

Pressure towards either termination and/or uptake of PGD, based on medical normalization or imputed cost-savings, has the potential to apply societal pressures on couples to act in violation of their personal values. It also risks increasing social or financial discrimination of those choosing not to act. A disproportionate focus on prevention over treatment for genetic disease also risks increasing the propensity for the discrimination of any individuals living with the condition.

Australia recently launched a government-funded national project offering carrier testing to 10,000 couples. The project aims to inform future reproductive carrier screening policy in Australia, including pathways for reimbursement, modes of service delivery, and addressing socio-ethical concerns. These concerns are not easily resolved, and require careful consideration going forward.

Education, Genomic Literacy, and Clinical Services

With the increasing interest in genomics, improving public awareness, genomic literacy, and workforce training are essential and require long-term government prioritization, funding, and political will. UK-based genomics initiatives, such as the 100,000 Genomes Project and the UK Biobank, have invested in education, public awareness, participant involvement, and workforce training, thereby facilitating a national dialogue on genomics. Comparable investment and resources are required elsewhere. In Australia, much-needed learning resources for medical professionals are under development as well as larger community-based efforts to achieve genomic literacy and encourage participation. Community engagement is vital to the success of any genomics initiative, and resources must be allocated to engage community views and build community trust.

The provision of clinical genetics services in Australia is inconsistent despite the growing demand, with imbalances between services in different regions and rural/urban locations. Trained genetic health professionals, especially genetic counselors, are typically in short supply. Education and training limitations, the rapid growth of industry, and the limited number of funded positions nationally contribute to this shortage. Current efforts to expand genomic workforces in Australia and elsewhere would require considerable expansion and increased workforce funding to optimize population-based testing.

A notable international example of developing the healthcare infrastructure required to accommodate population genomic testing is the Geisinger MyCode Community Health Initiative in the USA [2]. Geisinger is developing a model for "genome-first care" for adults who elect to have testing, as part of the healthcare system (as opposed to nationally reimbursed testing). MyCode has invested in genetic counselors, developing online resources, and integrating genetic services into primary care. Initially driven by the return of clinically significant results from biobank research sequencing, this has moved towards preventive clinical testing integrated into the healthcare system. MyCode provides a proof-of-concept for other healthcare systems to consider, yet many chal-

lenges remain regarding how to prepare and resource the wider healthcare system to manage the number of high-risk individuals identified by population-based testing.

Scientific/Technical Issues

An understanding of gene penetrance is one of the most notable scientific challenges of population genomic testing. The variable penetrance of adult-onset monogenic disease genes is an important concept to impart in clinical genetics practice, especially in predictive testing of asymptomatic people. Our scientific/mechanistic understanding of variable penetrance remains limited [21]. Penetrance estimates are influenced historically by clinical ascertainment biases towards affected families; large-scale quality phenotyping and longitudinal outcomes are required to improve penetrance estimates [22].

Variant curation and the interpretation of variants of uncertain significance represent another challenge, especially when considered at the population scale, across hundreds of possible monogenic disease genes for screening. International data/variant sharing initiatives such as ClinVar/ClinGen [23, 24] will be critical, yet are still evolving. Australian investigators have recently led notable efforts to address these challenges, including the Human Variome Project, the InSiGHT database (Lynch Syndrome), the Enigma Consortium (breast cancer genes), and many high-quality family-based registries of genetic disease.

Conclusion

The many possible benefits of population genomic screening can be realized if adequate health service scalability, public education, and ethical oversight are achieved, and technical/scientific progress continues. However, there will be considerable associated challenges for healthcare systems and society. Australia has made positive steps by developing a National Genomics Framework and launching disease-specific demonstration projects [7]. However, addressing the many challenges that lie ahead at the population level will require an ongoing concerted effort of the scientific and medical community as well as continued long-term government support and the trust and engagement of the public.

Acknowledgement

We acknowledge the contributions of Lei Zhang, Yining Bao, Moeen Riaz, Danny Liew, Xun Zhuang, David J Amor, Aamira Huq, Lara Petelin, Mark Nelson, Paul A James, and John J McNeil.

Statement of Ethics

The authors have no ethical issues to declare for this commentary article.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no funding.

Author Contributions

P.L. and J.T. conceived and wrote the manuscript. I.W. reviewed and edited the paper.

References

1 Zhang L, Bao Y, Riaz M, et al. Population genomic screening of all young adults in a health-care system: a cost-effectiveness analysis. Genet Med. 2019 Sep;21(9):1958–68.
2 Carey DJ, Fetterolf SN, Davis FD, et al. The Geisinger MyCode community health initiative: an electronic health record-linked biobank for precision medicine research. Genet Med. 2016;18(9):906–13.
3 Schwartz ML, McCormick CZ, Lazzeri AL, Lindbuchler DM, Hallquist ML, Manickam K, et al. A Model for Genome-First Care: Returning Secondary Genomic Findings to Participants and Their Healthcare Providers in a Large Research Cohort. Am J Hum Genet. 2018 Sep;103(3):328–37.
4 Grzymski J, Elhanan G, Smith E, et al. Population health genetic screening for tier 1 inherited diseases in northern Nevada: 90% of at-risk carriers are missed. bioRxiv. 2019 [cited March 27]. Available from: http://dx.doi.org/10.1101/650549.
5 Turnbull C, Scott RH, Thomas E, Jones L, Murugaesu N, Pretty FB, et al.; 100 000 Genomes Project. The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. BMJ. 2018 Apr;361:k1687.
6 Leitsalu L, Haller T, Esko T, Tammesoo ML, Alavere H, Snieder H, et al. Cohort Profile: Estonian Biobank of the Estonian Genome Center, University of Tartu. Int J Epidemiol. 2015 Aug;44(4):1137–47.
7 Stark Z, Dolman L, Manolio TA, Ozenberger B, Hill SL, Caulfied MJ, et al. Integrating Genomics into Healthcare: A Global Responsibility. Am J Hum Genet. 2019 Jan;104(1):13–20.

8 Gaff CL, M Winship I, M Forrest S, P Hansen D, Clark J, M Waring P, et al. Preparing for genomic medicine: a real world demonstration of health system change. NPJ Genom Med. 2017 May;2:16.
9 Rowley SM, Mascarenhas L, Devereux L, et al. Population-based genetic testing of asymptomatic women for breast and ovarian cancer susceptibility. Genet Med. 2019 Apr;21(4):913–22.
10 Lacaze P, Woods R, Zoungas S, McNeil J; ASPREE Investigator Group; ASPREE Healthy Ageing Biobank; and the STAREE Investigator Group. The genomic potential of the Aspirin in Reducing Events in the Elderly and Statins in Reducing Events in the Elderly studies. Intern Med J. 2017 Apr;47(4):461–3.
11 Haer-Wigman L, van der Schoot V, Feenstra I, Vulto-van Silfhout AT, Gilissen C, Brunner HG, et al. 1 in 38 individuals at risk of a dominant medically actionable disease. Eur J Hum Genet. 2019 Feb;27(2):325–30.
12 Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178–86.
13 Manchanda R, Patel S, Gordeev VS, Antoniou AC, Smith S, Lee A, et al. Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women. J Natl Cancer Inst. 2018 Jul;110(7):714–25.
14 Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al.; BRCA1 and BRCA2 Cohort Consortium. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun;317(23):2402–16.
15 Møller P, Seppälä TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D, et al.; Mallorca Group. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2018 Jul;67(7):1306–16.
16 Soerjomataram I, Lortet-Tieulent J, Ferlay J, Forman D, Mathers C, Parkin DM, et al. Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. BMC Med Res Methodol. 2012 Aug;12(1):125.
17 Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec;380(9859):2163–96.
18 Tiller J, Morris S, Rice T, et al. Correction to: Genetic discrimination by Australian insurance companies: a survey of consumer experiences. Eur J Hum Genet. 2019 Jul. DOI: 10.1038/s41431-019-0475-5.
19 Erlich Y, Shor T, Pe'er I, Carmi S. Identity inference of genomic data using long-range familial searches. Science. 2018 Nov;362(6415):690–4.
20 Benusiglio PR, Di Maria M, Dorling L, Jouinot A, Poli A, Villebasse S, et al. Hereditary breast and ovarian cancer: successful systematic implementation of a group approach to genetic counselling. Fam Cancer. 2017 Jan;16(1):51–6.
21 Cooper DN, Krawczak M, Polychronakos C, Tyler-Smith C, Kehrer-Sawatzki H. Where genotype is not predictive of phenotype: towards an understanding of the molecular basis of reduced penetrance in human inherited disease. Hum Genet. 2013 Oct;132(10):1077–130.
22 ACMG Board of Directors. The use of ACMG secondary findings recommendations for general population screening: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2019;21:1467–8.
23 Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, et al.; ClinGen. ClinGen—the Clinical Genome Resource. N Engl J Med. 2015 Jun;372(23):2235–42.
24 Landrum MJ, Lee JM, Riley GR, Jang W, Rubinstein WS, Church DM, et al. ClinVar: public archive of relationships among sequence variation and human phenotype. Nucleic Acids Res. 2014 Jan;42(Database issue):D980–5.