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EDITORIAL

Resource allocation in genetic and genomic medicine

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With the completion of the Human Genome Project, genome sequencing is now developing on a grand scale, with public and private institutions around the world investing in genomic technologies (IQVIA 2020, Phillips et al. 2021). Evidence is now emerging that the translation of next-generation sequencing (NGS) tests such as exome and genome sequencing into clinical practice may improve the diagnosis and management of genetic conditions, leading to better health and personal outcomes for individuals and families experiencing cancer or rare disease (Smedley et al. 2021).

However, integrating genomic medicine within national health services has so far not been straightforward (Sperber et al. 2017, Turner et al. 2020). Amongst other considerations, effective translation requires that careful attention is paid to issues surrounding priority setting and resource allocation. Commissioning genomic medicine services in a fair, equitable, and appropriate manner necessitates rigorous exploration of the ethical, policy, and practical implications, including factors such as cost, opportunity cost, clinical effectiveness, cost-effectiveness, need, ability to benefit, and procedural fairness. The challenge in priority setting and resource allocation is to find a way forward given these conflicting considerations.

Against this background, in June 2018, the Centre for Personalised Medicine at the University of Oxford organised a conference titled: "Resource Allocation in Personalised Medicine: Evaluation, Translation and Ethics" (The Centre for Personalised Medicine 2018). This event, organised in collaboration with the Health Economics Research Centre and the Ethox Centre, both at the University of Oxford, had three aims. The first aim was to describe and evaluate current and future developments in clinical commissioning structures, organisation, and delivery related to genomic medicine (The Clinical Context). The second aim was to summarise current developments and trends in assessing economic evidence relating to genomic medicine (The Health Economic Context). The third aim was to consider the international direction of travel in thinking about resource allocation related to genomic medicine (The International Ethics and Policy Context).

Speakers at the conference included Ellen Graham (NHS England), Tom Fowler (Genomics England), Inês Amado (Plan France Médecine Génomique 2025), Dean Regier (University of British Columbia, Canada), and Christian Munthe (University of Gothenburg, Sweden). Selected presentations are available to view at https://cpm.well.ox.ac.uk/term/resource-allocation-ethics-and-market. The conference facilitated fruitful multi-disciplinary conversations and sowed the seeds for future collaborations (for example, Genesolve (Genome British Columbia 2019)). At the same time, it was recognised that the issues debated at the meeting were of broad global relevance, and the content of the presentations and discussions should be disseminated beyond conference attendees to encourage a wider conversation about resource allocation in genetic and genomic medicine.

This Special Issue of the *Journal of Community Genetics* aims to advance discourse on this topic. This multi-disciplinary article collection examines issues surrounding resource allocation in genomic medicine from multiple perspectives. Six articles explore and describe best practice in resource

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allocation in this context, and highlight key challenges, particularly those that are generalisable internationally.

Weymann et al. (2019) is the first of a trio of articles considering the current evidence and challenges associated with allocating healthcare resources to genomic medicine from a specific national perspective, that of Canada (Weymann et al. 2019). The authors present a structured literature review on the economic impacts of NGS-informed personalised medicine in Canada, identifying a growing evidence base on the use of NGS panels in oncology. Although this aligns with current implementation of NGS-informed personalised medicine in Canada, the findings of many of these studies were subject to significant uncertainty. Moreover, evidence on the economic impacts of genome and exome sequencing was in short supply. The authors highlight three evidentiary challenges that must be overcome when generating evidence in the future, related to accounting for all NGS outcomes (including non-health outcomes), addressing uncertainty, and improving the consistency of economic approaches (particularly when RCT data are not available). Policies to share some of the reimbursement risk between payers and manufacturers may make it easier to allocate limited healthcare resources in this context going forward.

Lejeune and Amado consider a second national perspective, that of France (Lejeune C 2021). The translation of genomic testing into clinical practice in France is being driven primarily by the French Plan for Genomic Medicine 2025, which includes the development of a network of high-throughput sequencing platforms, and pilot research projects focused on cancer, rare diseases, common diseases, and sequencing in the general population. Economic studies evaluating the impact of this initiative on patients, caregivers, providers, and the health care system are a crucial component of this plan, and will inform healthcare resource allocation decisions throughout France. Lejeune and Amado describe a planned cost-effectiveness analysis of sequencing in patients with intellectual disability, highlighting potential contributions to the resource allocation evidence base, in particular new evidence on the cost of genome sequencing. Importantly, the authors highlight how standard health economic methods may be unable to quantify the non-health outcomes associated with sequencing that are important to patients and their families in France.

The third article considering a broad national perspective reports on the use of genome sequencing to diagnose rare diseases in Scotland (Abbott et al. 2021). Abbott et al. describe the Scottish Genomes Partnership, a national sequencing initiative that is aligned with the 100,000 Genomes Project in England, but run by clinicians, scientists, universities, and four regional genetics centres in Scotland. A key gap in the literature related to resource allocation in genomic medicine is evidence on the cost of both singleton and trio-based genome sequencing. Abbott et al. consequently make a significant contribution by estimating these costs to be £1841 per singleton and £6625 per family trio, although considerable variability by phenotype is noted, as well as the potential for economies of scale to reduce these costs further. A recurring theme in this Special Issue is that non-health outcomes may be as important as diagnostic yield for patients undergoing genome sequencing, and their families. Abbott et al. go on to present evidence from interviews with patients and families that identify several non-health outcomes as key benefits of sequencing, including the 'peace of mind' associated with ending a diagnostic odyssey, and the value that genome sequence data may provide to others in the future.

Two further articles describe how genetic and genomic tests are currently evaluated in health technology assessments (HTAs), and consider how robust use of real-world data could support HTA processes going forward. Norris et al. present a review and narrative synthesis of information extracted from assessments of genetic and genomic tests for heritable conditions conducted by the Medical Services Advisory Committee (MSAC) in Australia (Norris et al. 2021). Multiple methodological and policy challenges were identified across ten assessments, including how to incorporate stakeholder preferences for health and non-health outcomes of testing into these assessments, and how patient and community needs could (or should) inform decision-making thresholds. These challenges are not unique to Australia, but the resultant MSAC approach to decision-making in this context — characterised by pragmatism, a high tolerance for uncertainty, and flexible evidence thresholds — could usefully inform HTA processes in other countries.

Population sequencing initiatives such as the Genomics England 100,000 Genomes Project can provide valuable early evidence on the potential cost and health impacts of genome sequencing in a research context. However, the non-randomised nature of these studies precludes the use of some standard HTA methods to guide resource allocation. The fifth study in this Special Issue uses real-world data from Canada and quasi-experimental matching to potentially overcome these challenges (Weymann et al. 2021). In the context of genome sequencing to guide treatment in advanced cancer, Weymann et al. present a cost-consequence analysis that highlights scenarios in which sequencing may yield survival benefits at a cost lower than societal willingness-to-pay. Early economic evaluation of genome sequencing in a research context can reduce risk for many stakeholders before significant resources have been invested in test development (Abel et al. 2019); by refining and demonstrating novel methods to conduct these economic evaluations, Weymann et al. make a significant contribution to this literature.

Finally, Munthe considers resource allocation in translational genomic medicine from an ethical perspective (Munthe 2021). In many countries, the process of translating

genomic testing into clinical practice has required clinical and pre-clinical research to be integrated with routine healthcare. Munthe explains how this blurs the boundary between clinical and research ethics, and the way in which this translational process is organised can impact on resource allocation, and ultimately on whether investment in sequencing can be judged to be a cost-effective use of limited healthcare resources. The crucial distinction is whether it is the laboratory or the clinic driving the translational research agenda, and this can vary within countries and across different clinical contexts, complicating assessment. The broader resource allocation considerations that Munthe discusses — for example, the costs and benefits to society of government investment in novel life science technologies — have been largely overlooked in the health economics literature on genomics to date; improving this evidence base should be a priority going forward.

This Special Issue provides a snapshot of ongoing research into issues surrounding resource allocation in genetic and genomic medicine. Health economists and researchers in other fields who are investigating resource allocation in this context are making important contributions to this literature that are directly informing the translation of genomic medicine into clinical practice. The economic evaluation literature was limited 5 years ago but is now expanding rapidly (Diaby 2022, Goranitis 2022, Schwarze 2018, Simons 2021). Evidence is being generated on the health and non-health benefits of sequencing for different stakeholders (Buchanan 2019, Goranitis 2021). The appropriate economic methods to use in this context are under constant review (Bouttell 2022). Moreover, approaches to addressing funding challenges in different healthcare systems have been outlined (Phillips et al. 2021).

However, challenges remain, and these should drive future research on resource allocation in genomic medicine. First, appropriately valuing the health and non-health outcomes of health technologies is a persistent challenge at the intersection of economics and ethics in HTA and resource allocation, and is a challenge to which the example of genetic and genomic testing brings particular attention. The optimal approach is yet to emerge, although there may be merit in countries adopting an approach similar to the Australian model outlined by (Norris et al. 2021). Second, few studies have effectively included the wider economic impacts of genome sequencing in resource allocation analyses; an improved evidence base on this topic could help countries to make better informed decisions in the future regarding investments in sequencing capacity. Third, to date, resource allocation issues related to genomic medicine have largely impacted high-income countries. As the availability of testing grows in not just upper-middle-income countries but also lower- and middle-income countries, the health economic evidence base must also evolve, taking into account different values, preferences, and budgets (Phillips 2021, Wonkam 2021). Finally, researchers have so far been largely concerned with resource allocation in secondary care and beyond. The rapid recent emergence of multi-cancer early detection tests (Tafazzoli et al. 2022), intended for widespread use in primary care, will require researchers to increasingly consider resource allocation issues at the population level. The *Journal of Community Genetics* is an excellent home for research on all of these topics, and an article collection on "Resource Allocation in Genomic Medicine" will remain open beyond the publication of this Special Issue to receive all future submissions.

Declarations

Conflict of interest Sarah Wordsworth and James Buchanan are co-applicants of a project funded through Genome British Columbia's Genesolve programme and Illumina, and have received travel support from Illumina to attend conferences in Baltimore (USA), Barcelona (Spain), and Basel (Switzerland). Ilias Goranitis, Ingrid Slade, Angeliki Kerasidou, Mark Sheehan, and Katerina Sideri have no conflicts of interest to declare.

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