

Pathogen Genomics Into Practice Executive summary

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Executive summary

Pathogen genomics in this report is defined as the application of genome sequencing technologies to the characterisation and analysis of pathogens for the purpose of informing clinical and public health investigations of infectious disease. In principle, this technology has the power to transform the management of infectious disease in England.

Introduction

Pathogen genomic methods offer two key advantages over existing microbiological methods for investigating infectious disease:

- Whole genome sequencing can be used to discriminate between pathogens with greater sensitivity and often specificity than current methods, enabling outbreaks to be resolved or ruled out with greater speed, accuracy and confidence
- Genomic sequencing is an immensely powerful technology in that it can provide a description of a wide range of clinically and epidemiologically relevant characteristics of a pathogen, including identity, virulence determinants, drug resistance and relatedness to other pathogens. The 'generic' nature of genomes (which are all constructed from the same types of molecule) also means that the same technologies used for genomic analysis of one organism can, in principle, be applied to any other

Given sufficient understanding of the clinical and epidemiological significance of pathogen genome variation, this technology could in the future be used as a frontline tool in the analysis and management of most (if not all) of the pathogens that represent a threat to human health.

Can pathogen genomics improve patient and population health?

There is now a substantial body of peer-reviewed literature demonstrating how in principle pathogen genomics can be used to improve the management of infectious disease through improved diagnosis, detection and tracking of antimicrobial resistance and outbreak control. However, due to current limitations of genomic technology and of our understanding of the clinical and epidemiological significance of genomic variation for many important pathogens, utility of pathogen genomics, with the exception of tuberculosis and HIV, is currently limited almost entirely to use in outbreak detection and

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control. The vast majority of current diagnostic microbiology practice seems likely to continue in its current form at least until genomic technology improves to a point where it can deliver clinically useful results that compete with existing traditional microbiology methods on both turnaround time and cost.

Most evidence supporting the utility of pathogen genomics in microbiology practice centres around demonstrations of its ability to enhance the sensitivity and specificity of outbreak investigations, particularly for healthcare-associated infections (HCAIs) such as MRSA but also for community-acquired infections such as tuberculosis. However, from a health policy perspective it is vital to note that these investigations have mostly been retrospective and were unable to measure objectively their impact on patient and population health. This limits their value in determining whether use of pathogen genomics in real world clinical and public health settings would have resulted in significantly improved health outcomes for either individuals or populations. To do this would require prospective trials designed specifically to test the effectiveness of healthcare and public health service models that incorporate genomic information compared to existing practices.

As yet no such trials have been published, although several small scale, pathogen-specific pilot studies are now underway in England. Analysis of the results of such evaluations will be essential to determine whether infectious disease management services, informed by pathogen genomics, can be realised within our current health service operating frameworks. They will also help to determine whether the costs involved in establishing such services and tailoring clinical and public healthcare pathways to exploit them outweigh the benefits.

With this significant gap in the evidence base of effectiveness and cost effectiveness to support implementation, the case for the use of pathogen genomics relies on the assumption that the demonstrable improvements in analytical performance of this technology – compared to existing methods used for outbreak detection and investigation – are almost certain to deliver significant improvements in health outcomes. However, if the rate-limiting step in the performance of existing infectious disease management systems arises from care pathway factors outside of current microbiological practice, or if the major needs arise in diseases where testing is not currently amenable to improvement through genomic analysis, implementation of pathogen genomics may have little or no impact on health outcomes.

Developing a successful pathogen genomics informed infectious disease management system

Our project has reviewed the current state of science and clinical practice in pathogen genomics and gathered evidence from individuals working across the health economy, including health policy makers, clinical and public health practitioners and academic researchers developing genomic analysis tools. We have leveraged their expertise, in combination with the in-house expertise of the PHG Foundation in genomics and public health, to identify two objectives that the health system should seek to achieve in order to realise the potential benefits of genomics in the field of infectious disease management.

- **Ensure effective genomics service implementation and delivery, where this is justifiable on the basis of evidence, in the short term**
- **Drive innovation and expansion in the range of genomics informed / enabled services that can be developed and delivered in the long term**

What is key to achieving these objectives? The results of our research and analysis show very clearly that the effectiveness of any efforts to implement pathogen genomics will depend on the implementation of a nationally coordinated system of service development and delivery. We have identified two key features of this system that must be delivered if benefits of genomics technology to patients and populations are to be realised:

Data integration

Individual pathogen genomes cannot be usefully analysed in isolation. All clinically and epidemiologically meaningful information derived from pathogen genomes depends on our ability to compare them to other genomic data *e.g.* a pathogen genome isolated from a patient with the same disease. Equally it depends on our ability to combine the genomic data about a pathogen with relevant epidemiological information – for example when and where it was isolated and associated clinical information.

The timely collation, integration and sharing of genomic and clinical / epidemiological metadata across all parts of the health system involved in the delivery of pathogen genomics informed infectious disease services is therefore essential. This is particularly the case where we seek to realise benefits from this technology to deliver improvements in outbreak detection and resolution, where failure to share and integrate genomic and clinical data across different NHS and PHE laboratories will fundamentally undermine these efforts.

Not only will effective data integration serve to maximise the effectiveness of services that can be delivered now, such as outbreak investigation for certain HCAs, it is also essential for driving innovation and the expansion of services that need to be developed for future use. Accordingly, it will be vital that as much of the data generated by clinical and public health services as possible is made available to the research and development community. Access to such databases will enable them to increase understanding of the significance of pathogen genome variation and to develop the tools to analyse and interpret this variation that will become vital parts of future clinical and public health services. Although the development and refinement of analytic tools and methods can be accelerated by widening access to an integrated data resource, the widespread clinical deployment of pathogen genomics will be contingent on the availability of robust computational software for data analysis and adequate computing infrastructure. The development of accessible and automated computing software, underpinned by scalable and sustainable computational infrastructure, should therefore be prioritised by pathogen genomics service providers in order to support national use.

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Strategic coordination and leadership

Management of infectious disease and its impact on human health in England requires the input of a wide range of organisations including those with responsibility for public health (PHE and local authorities), delivering healthcare (NHSE), managing food safety (FSA) and animal health (APHA). It also depends on the input of a wide range of professional groups, ranging from infectious disease physicians, medical microbiologists and infection control nurses, to clinical laboratory scientists and academic researchers. Each of these organisations and professional groups has a stake in realising the effective development and implementation of pathogen genomics services. Consequently these efforts can only succeed where there are clear mechanisms to achieve strategic coordination of policy at an organisational level and where there are mechanisms to ensure that professional groups are supported to work together to share and develop the knowledge, expertise and best practice that will enable them to deliver the highest quality care to their patients and to protect the health of our population.

The roadmap

Within our report we detail – and provide evidence for – over 30 recommendations to support the achievement of the objectives set out above. We have presented these recommendations within the framework of a roadmap, which has two parallel routes to achieving patient and population benefit from pathogen genomics:

- Steps needed to achieve implementation of the pathogen genomics informed services for which we currently have sufficient evidence of utility, and the ability to deliver accurate and meaningful analysis to the clinicians and public health practitioners
- Steps needed to enable the research and development that will broaden the range of services that can be improved by the introduction of pathogen genomics in the longer term

We recognise that organisations and groups within the UK are already progressing along these paths. However, in their current form – focused on discrete service pilots for a selected number of pathogens, being deployed across a small number of locations, and involving only a limited proportion of relevant stakeholder organisations and professional groups – we believe they are unlikely to achieve the scale and depth of benefit that full-scale implementation of pathogen genomics could eventually bring.

The catalyst – enhancing service effectiveness now and accelerating innovation and service development into the future

As we highlight above, systems for effective data integration (that can be used for all pathogens and for all potential applications of genomics) and strategic coordination of policy and practice will be required to accelerate the rate at which genomics services are developed and implemented and to enhance the effectiveness with which they are delivered.

It is our view that these objectives can only be achieved through the development of a new, catalytic 'core' within this roadmap. We define the catalyst as: *A set of real or virtual structures that amplifies and integrates the current activities in pathogen genomics to accelerate and increase the effectiveness of their impact on patient and population health.*

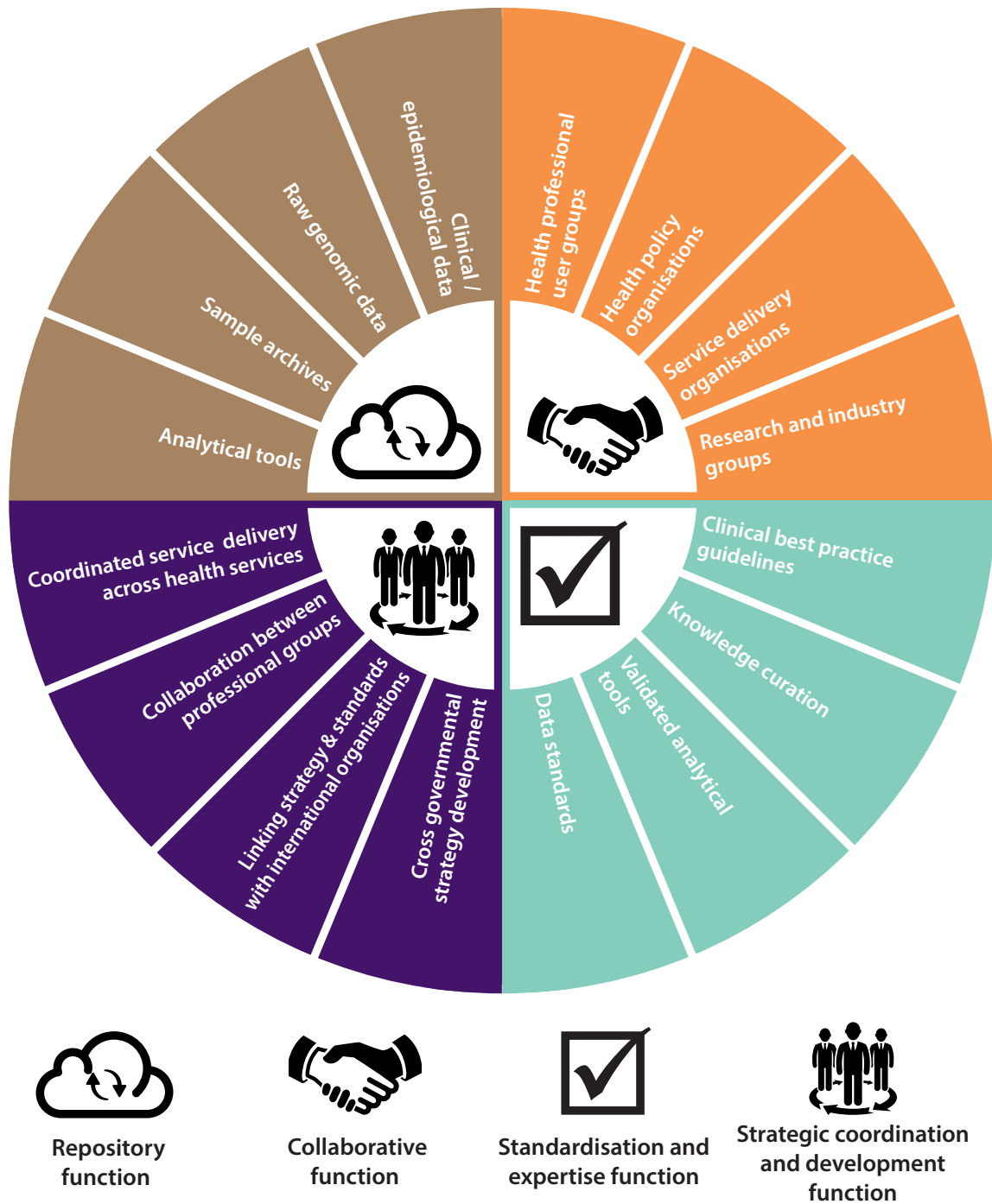
Our proposed catalyst performs four functions:

1. Infrastructure to provide a repository for data, knowledge and samples necessary to fulfil the data integration demands of the system
2. A focus for collaboration within and between the health services, academia and industry
3. A mechanism to facilitate development and diffusion of standards and sharing of expertise
4. Establishment of a leadership group that can oversee and drive forward the strategic coordination and development of policies and practices for the use of pathogen genomics across all relevant stakeholder organisations in England

It is the conclusion of our report that without the establishment of these functions many of the proposed benefits of pathogen genomics for patient and population health are unlikely to be achieved.

Enhancing service effectiveness and accelerating the rate of innovation and service development can only be achieved through the development of a new, catalytic 'core' within this roadmap.

Figure 1 Catalyst



Conclusions – an implementation dilemma?

Adoption and delivery of the roadmap – and in particular the catalyst proposed within this report – would require significant investment of resources by both policy and delivery organisations within the health system in England. Any decision to commit such resources will require sufficiently strong evidence to support the proposition that these investments would provide the anticipated returns in terms of health and economic benefits.

As noted earlier, there is currently a lack of direct evidence demonstrating that when implemented as part of real world pathways of infectious disease management and patient care, pathogen genomics can deliver on its promise. Furthermore, current implementation pilots, targeted at individual pathogens and developed in the absence of an integrated system-wide approach to data and knowledge integration and service delivery, are low risk but of limited reward as they are restricted in their capacity to generate this evidence. This limitation stems from the value and impact of pathogen genomic information being directly correlated with the amount of information available, the effectiveness with which it is integrated with other sources of information, its accessibility to innovators and the degree of coordination of the systems required to deliver services that rely upon it. The current absence of the systems necessary to meet these requirements significantly reduces the likelihood that the pilots will be successful in demonstrating positive health outcomes, and even where they do, their generalisability and wider adoption and diffusion across the health service will be severely hampered.

Continuing with the current gradual and fragmentary approach to implementation therefore poses a risk that must be acknowledged and addressed: it is less likely to generate the desired impact in terms of positive outcomes for patients and the population in England and is more likely to lead to less efficient use of resources within the health system than adopting the type of system-wide and integrated approach embodied by the catalyst we propose.

Conversely, we must also acknowledge that any decision to invest in building and operating the catalyst would entail taking a calculated risk, requiring its establishment prior to the availability of sufficient evidence to support all aspects of development. Nevertheless, it is the conclusion of our analysis that unless this risk is taken, the opportunity to realise the benefits of pathogen genomics for our population may well be lost.

Furthermore, if through its investment in genomics, England aspires to lead the world in precision medicine, then it must recognise that pathogen genomics, if implemented effectively, represents an opportunity to prove that genomics can truly 'transform' health services. UK scientists and clinicians have laid the foundations for this transformation, but the real challenge begins now with the need for health services leaders to direct and invest to establish the necessary systems and infrastructure to make pathogen genomics part of routine and effective clinical and public health practice. If they can achieve this, then they will truly lead the world.

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About the PHG Foundation

The PHG Foundation is a pioneering independent think-tank with a special focus on genomics and other emerging health technologies that can provide more accurate and effective personalised medicine. Our mission is to make science work for health. Established in 1997 as the founding UK centre for public health genomics, we are now an acknowledged world leader in the effective and responsible translation and application of genomic technologies for health.

We create robust policy solutions to problems and barriers relating to implementation of science in health services, and provide knowledge, evidence and ideas to stimulate and direct well-informed discussion and debate on the potential and pitfalls of key biomedical developments, and to inform and educate stakeholders. We also provide expert research, analysis, health services planning and consultancy services for governments, health systems, and other non-profit organisations.



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