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Phenotyping patients for genomic diagnostics



The realisation of genomic medicine in clinical practice rests on efficient and accurate interpretation of genomic data. Descriptions of a patient's clinical features - their 'phenotypes' - are essential to drive and target the correct analysis of this data. Maximising the benefits of genomic testing and managing the increasing demand for genetic tests depends on significant improvements in capturing and exchanging the appropriate phenotypic information across the NHS.

The term 'phenotype' has different meanings depending on the context - here we define phenotyping as the act of observing and recording a set of clinical features in the patient and their relatives (e.g. description, body measurement, medical histories). We discuss its role in the diagnosis and management of rare genetic disorders. Such systematic evaluation of patients is not a concept unique to genetics and genomics and occurs in most other clinical specialties.

The phenotyping process, the detail and consistency of data collected and its accessibility, will impact on the efficiency and quality of the diagnostic process.

Phenotype information is needed at several stages of the diagnostic pathway by different members of the clinical workforce for the generation of a clinical report. This information, together with the genetic data, constitutes the core evidence upon which a patient's diagnosis is made. Therefore the phenotyping process, the detail and consistency of data collected and its accessibility, will impact on the efficiency and quality of the diagnostic process. To facilitate the timely introduction of genomic sequencing in the clinic all these aspects of phenotyping require consideration and adaptation with pragmatic implementation of changes to clinical practice.

Phenotyping: current practice

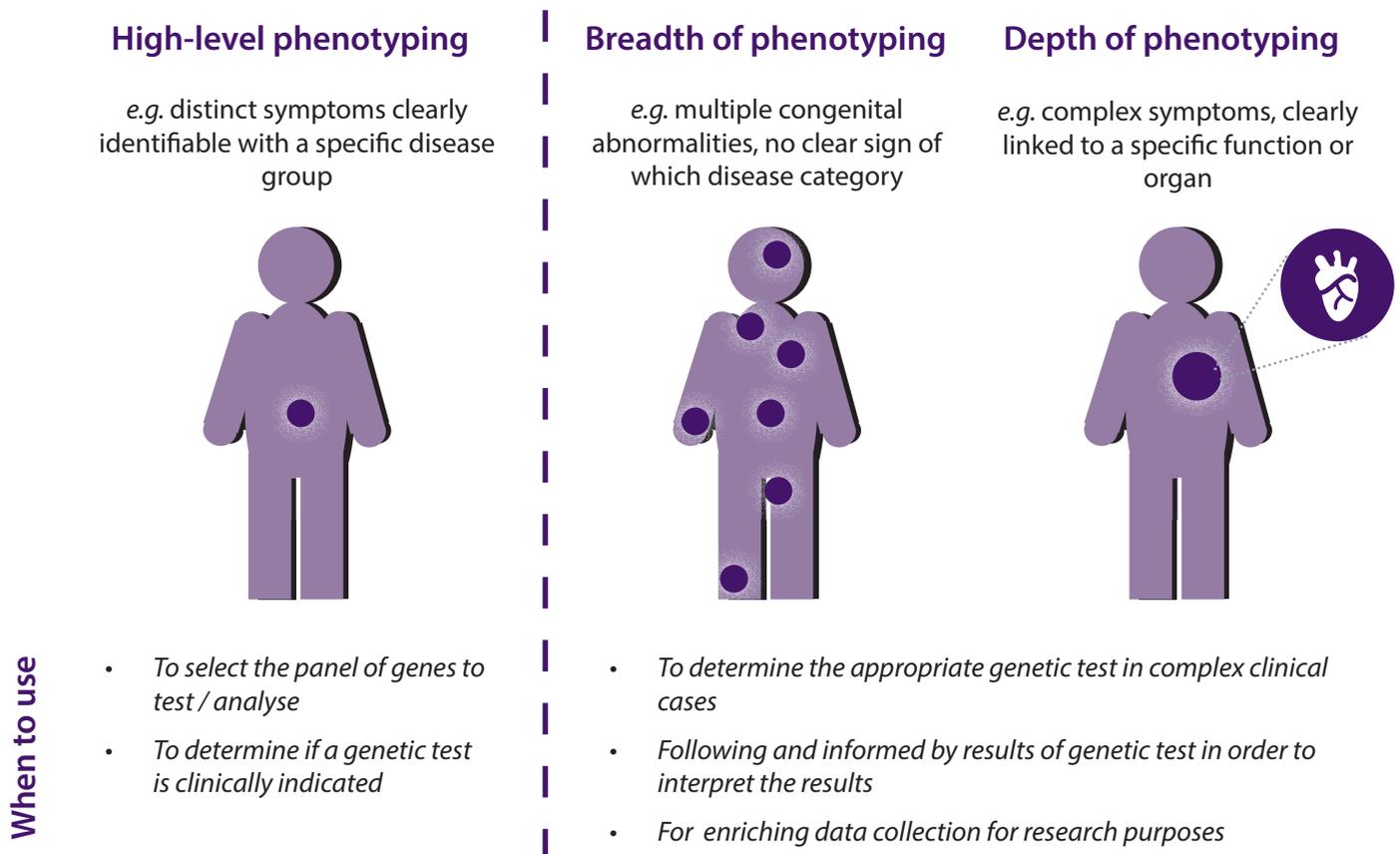
Who does it?

Phenotyping is routinely performed in a range of clinical specialities, for example a patient presenting with onset of blindness will likely be examined by an ophthalmologist; infants with dysmorphic features are likely to be examined by paediatricians or clinical geneticists. In both cases, phenotypic investigations will initially be restricted to those features that relate to the presenting complaint, and any related diagnoses that the clinician is aiming to rule in or out.

How much and when?

Phenotyping can occur before and after genetic testing, however the depth and breadth of phenotyping required depends on the circumstances of each individual patient case (see figure below).

Figure 1: Types of phenotyping and their applications



Who uses it?

All clinicians can use the patient phenotype information generated by different specialists to direct subsequent clinical testing. A clinician referring the patient for genetic testing will use the information to inform the appropriate choice of genetic test and a clinical scientist performing the test will use it to guide the accurate analysis of genetic data.

How is it recorded and transmitted?

Often this data is recorded in patient's notes and forwarded in descriptive referral letters or forms, although many specialities do use standard medical coding to record observations. There are a number of challenges with collating and sharing phenotype data; the information is often dispersed across the healthcare system and is difficult to locate and extract; descriptive, non-coded data can be open to misinterpretation. Additionally, phenotype and genotype information are collected by different people in the testing pathway and are therefore often stored in different places.

What needs to change?

Improved mechanisms for capturing and sharing phenotypes - the systematic and electronic capture of phenotypes using standardised language by the clinician referring a patient for genetic testing will aid its accessibility by clinical scientists and linking with genotype data. Ultimately, the improved aggregation and exchange of phenotypes will advance the application of genomic medicine by:

- Enabling the correlation of phenotypes with genetic variation, and thereby informing future clinical management of patients
- Increasing the power of genetic analysis for very rare undiagnosed conditions by enabling the identification of multiple unrelated patients with similar manifestations
- Aiding improvements in clinical pathways, through auditing of data e.g. pick-up rates of genetic disorders by a given phenotype

Balancing the phenotyping approach - as demand for genetic tests increase, the timing, breadth and depth of data collection will require consideration. Decisions as to the extent of phenotypic information to be gathered prior to the genetic test should continue to be made on a case by case basis. Extent can also depend on purpose - data generated for a large scale research initiative may require earlier and greater depth of phenotyping in a single episode than what might be necessary or feasible in a frontline healthcare context with finite resources.

Records of phenotype data are often difficult to access and the narrative open to misinterpretation.



Standards to describe phenotypes

Phenotyping to facilitate genomic medicine - standards and software tools should be integrated into healthcare services in a way that supports clinical end-users. Exhaustive standards and unwieldy tools could lead to delays, poor compliance and fewer patient referrals.



Tools to enable systematic capture of phenotypes

Phenotyping fit for genomic medicine - what's needed?

The amount of data collection required for delivering a clinical service should be assessed for different disease scenarios - extensive, detailed phenotyping prior to the genetic test may not always be necessary, nor economically efficient. As the cost of genomic tests falls and knowledge of genetic variation increases, the process of genotyping and phenotyping may become more iterative, simplifying the use of genetic information to inform the choice of clinical investigations.



Better exchange of phenotype data

Adequate computational tools which capture the range of phenotypic features and across different organ systems in standardised formats need to be adopted - software already trialled in healthcare systems^{1,2,3} could be deployed. Additionally, mechanisms to extract data from health records are needed to facilitate phenotyping and give end-users a detailed clinical picture when assessing patients or their genetic data.



Purpose defines degree of phenotyping

Curation and sharing of phenotypic data in a resource linked to genetic data is needed to improve genomic data analysis - since phenotypic data is potentially identifiable data, it should be collated in a managed-access resource to safeguard patient privacy.

Standardised descriptions of phenotypes should be adopted for accurate comparison and exchange of patient phenotypes - consideration should be given to the level of detail required from standardised descriptors; simple controlled terms will be easier to manage and adopt.

Providing adequate infrastructure to facilitate the delivery and embedding of tools and resources - to extract, capture, store, and exchange phenotypic data will require commitment and investment from healthcare providers and commissioners.

References

1. Girdea M. *et al.* Hum Mutat. 2013; (8)1057-65.
2. Wright C. *et al.* The Lancet. 2015; (14)61705.
3. <http://compbio.charite.de/phenomizer/> [Internet] Accessed 18 May 2015.

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