Bioethics of Whole Genome Sequencing and Exome Sequencing

Exome sequencing (ES) and whole genome sequencing (WGS) putatively identify all **adverse functional alleles of protein-coding genes**.

- Gene discovery
- Causative mutations can be identified
- novel genes and disease mechanisms uncovered
- phenotypic implications of both known and novel genetic variants

When studying a disease in which the list of associated genes is comprehensive, WES presents a high success rate pinpointing the causative mutation.

For example,

- one can sequence only the protein coding regions of the genome (the exome), which is referred to as whole exome sequencing (WES), or
- one can sequence only certain gene families (e.g.: globin genes) or genes involved in a particular biological pathway or associated with a particular (set of) disorder(s) (e.g.: colon cancer).
- enable the capture of the full extent of genetic variation in an individual's genome or their entire gene coding region respectively.
- WGES studies are therefore extremely diverse in nature and will play an essential role in determining the genetic aspects of human disease susceptibility, risk of complications, modifiers of disease severity, outcomes and response to therapy (including drug response).

- The applications for **transcriptome** and **epigenetic** studies also raise practical and ethical issues that are related to and overlap with germline DNA sequencing and the study of variations (which is, presently, the most popular subject of debate when it comes to discussing WGS)

- Due to the large-scale, collaborative nature of WGES studies, ethical and legal issues are of increasing concern and have important implications for society.

- The right to privacy encompasses the right to control the dissemination of information about one’s private life.
- Large amount of data made publicly available through WGES studies does pose a potential threat to the privacy of individuals participating in such studies, where true anonymisation cannot always be guaranteed.

Limitations of WGS and ES

- sequencing errors,
- uneven exome capture,
- incomplete coverage and
- short read length
- lack of access to a public database and inability to share the ever-growing accumulating data
- In the case of complex diseases or there is a lack of knowledge regarding the set of associated genes, WES will present much lower initial success rates
- filtration of variants: WES usually results in tens of thousands of variants per patient, which should be filtered down to a reasonable amount in order to pinpoint the one, correct, causative variant

How use of ES/WGS challenges

(i) models under which informed consent is typically obtained

(ii) how harms associated with data sharing are considered

(iii) the nature of obligations surrounding unanticipated findings

Ethical Issues

1- Informed consent

2- Data handling/sharing

3- The return of the results

1- Informed Consent

- It is crucial to convey an accurate presentation of the capabilities and limitations of this technology.
- Informed consent is a cornerstone of ethical research conduct and aims to protect research subjects against coercion, deception and abuse
- Meaning of the terms ‘disclose’, ‘ return’, ‘communicate’ and ‘ share’.

- Genomic studies involving human research subjects typically require ethical clearance from relevant institutional review boards (IRBs) or research ethics committees (RECs) before commencing (EMU Ethical Committe)
- informed consent from study participants to ensure that these individuals are able to make informed decisions regarding potential risks and benefits of voluntary participation
- an on-going process
- should engage prospective study participants in frequent discussions about the research, give them adequate time to decide whether they wish to participate in the proposed research, ensuring that participants realise that participation is voluntary.

- The informed consent document should contain a variety of different elements presented in a concise manner to ensure that participants can easily comprehend the text
  - brief description of the project,
  - the goals of the research,
  - the potential risks and benefits of participation,
  - return of results,
  - options for withdrawal from research and
  - data sharing plans.
- in accessible language
- adequate readability and comprehensibility of informed consent forms

Matter of Consent of Minors and Incapacitated Adults

- The discloser of results to the participant's guardian is restricted to clinically implicated findings
- The standards for clinical genomic sequencing recognize a distinction between providing SFs to adults versus children and adolescents
- Sequencing data obtained from a minor could be widely shared before they reach an age to self-determine data sharing limits, diminishing their autonomy as adults

Challenges..

- the potential information overload,
- the complexity of information,
- the limited ability of individuals to sufficiently understand and or remember the information given,
- biased understanding, and
- false hopes.

Additional issues that are specific to genome analysis, including the vast volume and complexity of genetic information and the possibility of generating information about the future health status or the health risks of relatives are likely to complicate the informed consent process further when WGS is introduced.

Questions include what information should be included in the process, how should it be performed and is it possible to perform it with the same notions traditionally used in genetics?

- One of the major reasons for concern is the high level of uncertainty regarding the outcome of the eventual analysis
- Secondly introduces the need to determine which results will be returned to research subjects and patients
- the consent process offers important opportunities to discuss the return of results, to be, respectful of the ‘right not to know’ and the wish to not be informed about particular genetic information
- Thirdly, information may have relevance or implications for relatives, who are not involved in the informed consent process
- Fourthly, the open-ended potential for further use of data

Recommended elements to be included in the informed consent form and process for the clinical use of WGS

- pre-test counselling,
- scope of the test,
- description of the test process,
- expected benefits,
- possible risks,
- voluntary nature of participation,
- possibility of refusal at any time,
- description of alternative diagnostic methods,
- confidentiality and privacy,
- informing relatives or not,
- the inclusion of patient data in databases,
- storage and future use of samples,
- management of incidental findings and specific informed consent

Key point	Description
1. Description of WES	Briefly describe WES and analysis
2. Purpose for WES	State how the data will be used
3. Benefits and risks of WES*	Define potential benefits and risks of the procedure
4. Uncertainty of results*	Explain the limitations of testing
5. Follow-up if results are up-dated	Describe laboratory policy regarding re-contact of referring physician and/or patient as new knowledge is gained about significance of partic ular results
6. Results returned to whom	State to whom the findings will be communicated
7. Describe results returned to proband*	Explain the scope of data and information that might be returned to the individual
8. Results excluded from report*	Explain types of results that will not be returned
9. Define SFs*	Define the secondary findings that are possible, or likely, to arise or be sought from the procedure
10. Options for ACMG minimum list results*	Describe the laboratory policy for disclosing the ACMG minimum list

Content analysis coding ACMG & bioethics commission recommendations matrix. (Table retrieved from; Fowler A.S., ET AL. J Genet Counsel (2018) 27:104–114)

11. Return SFs for minors*	Describe steps to be taken upon discovery of secondary findings for minors
12. Disclose SFs to relatives*	Explain steps to be taken upon discovery of secondary findings with potential implications for family members
13. Disclose carrier status for recessive disorders	Explain options for receiving information derived indicating carrier status for recessive disorders
14. Sample may be shared in databases*	Request permission to provide individually identifiable results to databases
15. Request to use sample for research	Request permission to use the data for research purposes
16. Who has access to sequence data	Describe who has access to the data generated in the course of clinical WES
17. Opportunity for genetic counseling	Describe the options for genetic counseling
18. Risk discovering misattributed parentage	Explain laboratory policy for providing information indicating misattributed parentage

Content analysis coding ACMG & bioethics commission recommendations matrix. (Table retrieved from; Fowler A.S., ET AL. J Genet Counsel (2018) 27:104–114)

- The primary aim of research is to generate data that advance science, often also without generating a direct benefit to the research subject and this is reflected in the informed consent document.
- However, it is well known, that a ‘therapeutic misconception’ (the mistaken assumption that research will yield a direct therapeutic benefit to the participant) may occur in research participants (which, for genetic research could likely be a diagnostic or screening misconception as well).
- Therefore, during the informed consent process, researchers should make clear **the goals of the research** and attempt to dispel any misconception on the part of the participant.
- The primary aim of WGS in clinical care is different, namely reaching molecular diagnosis, and therefore the reasons for consenting to WGS or generating and returning specific results may differ

2- Data Handling/Sharing

ethical issues in archived samples and data

‘When is re-consent indicated for previously collected samples-data ?’

- re-consent in the context of archived data
- subjects give an initial consent at procurement regarding various aspects of the data collection and banking.
- When a researcher is interested in utilizing the data in the archive, the subjects are approached again and a more classical informed consent is required. (problematic due to changing states of the subjects, costs and logistics)

Informed consent in biobanks

Biobanks: infrastructures leading to organized way of gathering, storing and using samples, thereby creating a new resource with various objectives and very long-term use.

This requires a much broader consent from the patients comparing with the specific informed consent needed in biomedical researches.

Most people do not want to be asked for consent, but they do need to feel that the system is sensitive for their issues and transparent to them.

They wish to know what is going on and receive all relevant information

Data Handling

- WGS is expected to reveal three to four million variants, WES is expected to reveal about 20 000 variants.
- Handling such a vast amount of data brings to the surface various ethical and practical concerns.

  (i) storage, (ii) analysis, and (iii) sharing of data or results.
- whether and how long data should be stored are very pertinent.
- In some situations re-sequencing may be a better option than storing data (i.e. if safe storage of the data cannot be guaranteed, if sequencing quality increases greatly in the future, and/or it becomes very inexpensive)
- Stored data create real identification risks and therefore the potential for breaches of privacy and confidentiality

- For example, it must be clear whether there is an obligation for record keeping of (all)WGS data and analyses, and if so, under what circumstances, and to what extent such an obligation exists?
- Should minors, for example, be able to access results from WGS once they reach the age of majority if data were generated many years earlier?
- Moreover, should people be re-contacted for the purposes of looking at new diagnostic or treatment options that have become available since the initial sequencing was performed (which obviously can only be done if data have been stored)?

- Getting meaningful information and interpretation is important
  - i.e. relevant for obtaining a diagnosis or answers to a research question
  - out of the three to four million variants that are identified through WGS requires analysis and interpretation.
- Bioinformatic analysis
  - comes with significant financial cost, which may exceed the technical costs of WGS many times
- Financial issues may raise serious concerns about the feasibility of reimbursement and equitable access for all, and introduce new problems of distributive justice.

Data Sharing

- Concept of data sharing through databases to allow for the secondary use of data
- Should be included in the informed consent document
  - For example, the more sharing of information about variants found in patients with similar phenotypes, the greater the power or basis there is to properly classify variants.
- It is important to promote and facilitate ethical sharing of data and results and to ensure that there are just measures for recognition should publications result from shared data
- People want to be informed on data sharing plans, and lack of transparency may impair individual and public trust in WGS
- Data sharing may increase the risks of having of individuals identified and is related to the breach of privacy and confidentiality previously mentioned with respect to informed consent

Participant identifiability

- The privacy risks associated with WGES data sharing are increased due to the scope of these data
  - include information on rare alleles
  - variants of clinical utility that will aid in re-identification of samples
- the tools to analyse WGES data allows profiling of identifiable phenotypic traits and Mendelian diseases,
  - easier to re-identify due to their rarity and unique pedigrees that are often included in publications

Return of research results and secondary/incidental findings

- Results may vary considerably in clinical validity, clinical utility and actionability.
- This has important implications for the return of results.

Should results, for example, be returned when they cannot be acted upon?

- Due to the fact that WGES technologies efficiently analyse the entire genome and exome respectively; secondary, incidental or unrelated findings that were not part of the original research hypothesis may be encountered, which places emphasis on the researchers' duty to in form participants of such results.
- The dilemma faced by genetic/genomic researchers in handling such findings is not new, yet the scope of the results generated by WGES exponentially amplifies the probability of encountering these findings exponentially

- The moral duty to warn research participants of secondary/incidental variants of interest
  - needs to balanced against opposing duties such as the limits of beneficence,
  - excessive burdens on researchers, and
  - the fact that returning results may be harmful
- If an option to return secondary/incidental findings to research participants will be given in a study, it is important to determine what results can justifiably be returned to these individuals in order to minimise risks and increase benefits of such a practice.
- Researchers must determine which type of genetic variants should be returned to research participants.

(This is particularly challenging with novel variants, which is highly relevant for WGES research)

(1) the right to information about oneself,

(2) the potential of positive health outcomes due to the personal meaning subjects give to the information,

(3) the establishment of increased trust in the genetic research,

(4) reciprocity towards research subjects, and

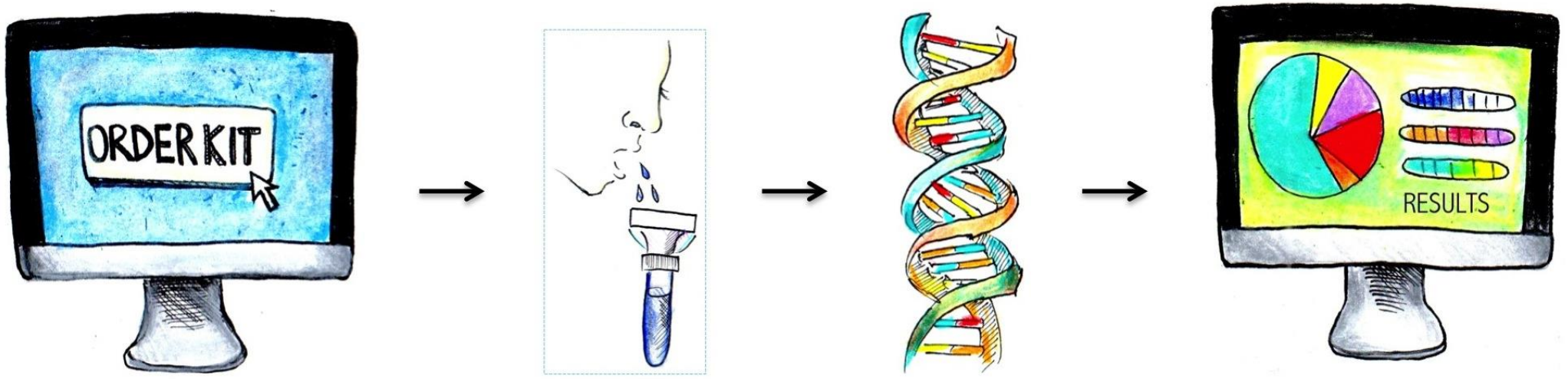
(5) the expression of respect towards research subjects

need to avoid therapeutic misconception, the risk to cause harms and burdens (e.g. stress and anxiety), and the lack of research subjects' ability to understand the results.

GWES vs GWAS

- In this regard, it is important to draw a distinction between GWAS and WGES studies.
- GWAS-associated loci for most diseases are often associated with small-to-moderate risk and have low predictive value for an individual.
  - Therefore, their clinical relevance and potential for being actionable are quite limited.
- WGES studies on the other hand often find coding mutations with large effect sizes, some of which are already annotated as disease-causin
- **healthy individuals carry, on average, approximately >2 robust disease-causing mutations in their genomes**

Bioethics in Diret-to-Consumer (DTC) Testing



- Direct-to-consumer (DTC) genetic testing refers to any form of genetic testing sold directly to consumers without the involvement of a medical professional.
- Consumers are sent a buccal swab as part of a kit, which they return through the post.
- This sample is then analysed for several thousand different single nucleotide polymorphisms (SNPs) at various genomic loci, in order to provide information about the individual's genetic constitution.
- The market for such tests is competitive, and currently occupied by a variety of different companies, such as 23andMe, Atlas Biomed and EasyDNA.

- In DTC genetic testing, a consumer directly orders a particular type of genetic test by sending specimen via mail to a laboratory or company, which in turn creates their genetic profiles according to the request and then sends it back to the consumer.
- People choose DTC for three purposes:

1. To gain information about their ancestry
2. To know their susceptibility towards certain diseases or risk factors
3. Just for the curiosity on their genetic makeup

- After testing, the company sends the result to the consumer via mail or internet sources.
- The process completes without the presence of physician or genetic counselor.

DTC genetic tests might provide a range of health information:

- Polygenic risk scores
- Genotype at specific points
- Carrier screening
- Uninterpreted “raw” genetic data

Limitations of DTC genetic tests?

- Predictive value is low when there is no family history of disease
- False positives are common, especially where third party interpretation services are used
- Reassuring results can be false negatives

Concerns about DTC

- Individual possible psychological harm,
- Information communication,
- Lack of professional counselling,
- Confidentiality of the genetic information
- Lacking data protection and opaque data protection policies
- Lacking validity and clinical utility of test results
- Quality assurance and reliability
- Price of the test and related services
- Lack of legal regulations

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