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# Meeting summary: ethical aspects of whole exome and whole genome sequencing studies (WES/WGS) in rare diseases, Tel Aviv, Israel, January 2013

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**Summary**

A recent E-Rare workshop reviewed the ethical aspects of whole exome and whole genome-sequencing studies (WES and WGS, respectively) in rare diseases. Leveraging new genomic technologies, which output vast amounts of known and novel genetic variants, researchers are learning more about the genetic basis and mechanisms involved in rare diseases. In some cases, these findings are translated into diagnostic tools for the benefit of rare disease patients. Among the disclosed data, which can assist in treatment management, incidental findings await, bringing with them ethical concerns for the clinicians, researchers and patients.

The Chief Scientist Office of the Health Ministry of Israel, a member of E-Rare Consortium, organized a workshop in Tel Aviv on January 2013, dedicated to 'Ethical aspects of exome and whole genome-sequencing studies in rare diseases'. The workshop gathered top-level specialists in ethics, law and clinical and diagnostic genome/exome sequencing, all applied to diagnosing and treating rare genetic diseases.

Following the opening session [chair Prof. Béla Melegh (Pécs, Hungary)], the meeting had three main themes: (i) the nature of informed consent in the era of WES/WGS studies [chair Professor Rivka Carmi (Beer-Sheba, Israel)], (ii) archived samples and data [chair Professor Amos Shapira (Tel-Aviv, Israel)] and (iii) ethical and legal aspects of WES and WGS at the European level [chair Dr Monica Ensini (Paris, France)].

The opening session of the workshop included lectures by Professor Thomas Meitinger and Professor Orly Elpeleg. Professor Meitinger (Neuherberg, Germany) reviewed successful implementations of WES in rare disease research, in which the causative mutation was identified and novel genes and disease mechanisms were uncovered (Ng *et al.*, 2009; Haack *et al.*, 2010, 2012; Johnson *et al.*, 2012). The technology available to read DNA at vast amounts is common and available in many laboratories these days. However, there are still limitations to these technologies, such as sequencing errors, uneven exome capture, incomplete coverage and short read length. The major bottleneck for progress in the field is lack of access to a public database and inability to share the ever-growing accumulating data. Professor Orly Elpeleg (Jerusalem, Israel) presented the flow and use of deep sequencing information from research to the clinics. Exome sequencing is a gift, she says, in many medical aspects. WES is already clinically applied in many centres for the molecular identification of causative variants in known disease-associated genes. Additionally, WES extends the phenotypic implications of both known and novel genetic variants (Zhou *et al.*, 2012). When studying a disease in which the list of associated genes is comprehensive, WES presents a high success rate pinpointing the causative mutation. However, when the disease in question is either complex or there is a lack of knowledge regarding the set of associated genes, WES will present much lower initial success rates. For example, a recent study on intellectual disability, in which the list of associated genes is far from complete, correctly identified pathogenic mutations in known genes in only 16% of the cases (de Ligt *et al.*, 2012). One of the biggest challenges in WES data analysis is the filtration of variants. WES usually results in tens of thousands of variants per patient, which should be

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filtered down to a reasonable amount in order to pinpoint the one, correct, causative variant. Since it is very easy to provide false positive data in the genomic era, the investigator must follow the initial identification in the laboratory and provide proof for the direct association between the variation and the phenotype. The most appropriate validation is finding another patient with a different mutation in the same gene. Additional possible conformations are checking the function in an *in-vitro* system or generating an animal model.

Following the opening session, the first theme examined the complexity of informed consent in WES and WGS studies. Dr Vardit Ravitsky (Montreal, Canada) talked about establishing informed consent in the research or diagnostic laboratory. In her talk, Dr Ravitsky elaborated on specific elements conveyed to research participants that require modulation in the context of WGS. It is crucial to convey an accurate presentation of the capabilities and limitations of this technology. Dr Ravitsky described the various ways analysis results are conveyed to a patient by revising the meaning of the terms 'disclose', 'return', 'communicate' and 'share'. Each specifying a different feedback supplied to the patient. Additional modulations include a more dynamic consent approach, in which the patient may monitor the data and alter allowance of information to be shared or used in different times in order to maintain confidentiality. Finally, the issue of discloser was addressed, with 'incidental findings' posing the biggest challenge. There is currently a consensus to disclose scientifically valid, clinically actionable results that the participant desires to know. However, an ongoing debate exists regarding the definition of clinically relevant information (Berg *et al*., 2011) and how to address the participant's desire not to know. Also, the lecturer defined the investigators complexity to decide what results to disclose, when the findings do not correlate to the participants informed consent.

Professor Susan Wolf (Minnesota, USA) elaborated on the issue of dealing with incidental findings (IF). Specifically, she questioned the dichotomous architecture of researchers versus clinicians and their role in WGS studies. Professor Wolf used a metaphor, describing a river, where research and clinical aspects are located on opposite banks. Individual research results (IRR) and IF are discovered on the research bank, and the main challenge addressed in the talk is what information may or should be bridged over to the clinical side. Currently, there is a multitude of guidelines regarding doctor–patient relations that emphasize the doctor's duties and obligations towards the patient. Contrary to this, ethical guidelines in the researcher–participant relation contain very little clinical duty and the pursuit of knowledge plays a much bigger role. Currently, WGS and WES undermine the division between researcher and clinician duty. The abundance of data produced by these technologies routinely results in vast accumulation of clinical information. There is an increased obligation for the researcher to disclose certain findings depending on their implications. The researchers' obligation to return findings to the participants is solemnly based on trust. However, the trust given to the researcher is hedged by various parameters out of the scientific-research scope. These include limited funds to deal with the clinical aspects of the study; diversion of resources from the main objective (research); lack of clinical expertise; and, confusion of the participants themselves between the role of the researchers and the clinicians.

Professor Wolf published the recommendations for the researcher describing IRR and IF management in Medical Genetics (Wolf, 2012; Wolf *et al*., 2012). Reporting recommendations were divided into two main bins, those that 'should' be shared with the participant and those that 'may' be shared. The investigator should report back when IF or IRR are analytically valid and compliance with law, reveal established and substantial risk of a serious health condition, are actionable with potential to alter ones course and if consented by the participant. The researcher may return additional findings if they reveal established risk of likely health condition or influence reproduction and personal utility. Another reason to return results is if the return is likely to provide net benefit to the patient.

In the final lecture of this theme, Adv. Talia Agmon (Ministry of Health, Israel) introduced the matter of consent of minors and incapacitated adults. The law allows including these population in genetic studies and medical research only if participation directly benefits them, it is in their best interest and there is no other way to do the study. WGS differs from traditional genetic testing due to its high-throughput of findings, most of which are neither clinically applicable nor linked to the phenotype studied. Therefore, the discloser of results to the participant's guardian is restricted to clinically implicated findings. In order to facilitate future integration in minor and incapacitated adults research, Adv. Agmon recommends a revision of recruitment and discloser policies and establishment of a periodic re-consent and follow-up procedure.

The second theme involved the ethical issues in archived samples and data. This part consisted of three lectures: Professor Nils Hoppe (Hannover, Germany) answered the question 'When is re-consent indicated for previously collected samples-data?' He presented the current standard of re-consent in the context of archived data, in which 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. This state is problematic due to changing states of the subjects, costs and logistics.

Subsequently, Dr Emmanuelle Rial-Sebbag (Toulouse, France) presented principles of informed consent in biobanks. She defined biobanks as 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. In 2012, a new report on biobanks was published (http://www.publichealth.ox.ac.uk/helex/news/new-report-on-biobanks-by-the-european-commision-expert-group) by a commission expert group (including Dr Emmanuelle Rial-Sebbag). The report addresses the issues of biobanks not only from the legal and ethical point of view, but also from a scientific, social and humanities point of view.

Finally, Professor Ephrat Levy-Lahad (Jerusalem, Israel) discussed research on archived samples in WES/WGS studies. The advantages and disadvantages of using archived samples as opposed to biobanks were pointed out. The main question of the talk was regarding the ethical basis for requesting consent for use of archived samples (Savulescu, 2002; Stegmayr & Asplund, 2002; Van Diest, 2002; Bathe & McGuire, 2009; Vermeulen *et al.*, 2009). According to Professor Levy-Lahad, the researcher–participant contract should be one of donation, giving a sample for research for general good, not for personal gain. In the context of using the archived samples, Professor Levy-Lahad thinks the ethics committee who has moral and legal obligation to the samples, and not the patient, should be the one to agree for further sample usage. The committee will determine whether there is reasonable likelihood for the research to achieve scientifically beneficial data that would be difficult to get otherwise. Also, in the case where there is no participant consent, the committee will decide whether the patient would be harmed in terms of confidentiality. Only if the risk is minimal, and it is not practical to re-consent, may the researcher access the archived samples. She summarised the lecture by mentioning that 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.

The third theme dealt with ethical and legal aspects of WES and WGS at the European level. Dr Simon Woods (Newcastle, UK) discussed the state of legal and regulatory frameworks for WES/WGS at the European level and Dr Tessel Rigter (Amsterdam, the Netherlands) revised European initiatives for unified informed consent.

## Concluding remarks

Genome sequencing is a gift for the clinicians and allows their unbiased view of a particular syndrome or phenotype. Therefore, a clinical genetic view of the known or novel variants might assist in treatment management of rare diseases requiring better study models. However, numerous ethical issues arise when this vast amount of data is being collected and analysed, and IF are encountered. Therefore, there is a need for tight legal regulation at the local, European and international levels.

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