Presidency of the Council of Ministers

MANAGING "INCIDENTAL FINDINGS" IN GENOMIC INVESTIGATIONS WITH NEW TECHNOLOGY PLATFORMS

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Introduction

In this new document on human genetics the NBC deals with the bioethical issues raised by the rapid evolution of second generation genome sequencing techniques, which over the recent years have transformed and speeded up research on and the diagnosis of many illnesses. These new techniques have posed the need for new shared guidelines and, in particular, standardised regulations for managing the so-called incidental findings, both at clinical and research levels.

Following a description of the state of the art, the NBC goes over a number of crucial ethical steps of the debate with particular reference to the discussion on the theoretical foundations of the 'right not to know' in a genetic context.

Even though aware that this transition from basic knowledge to clinical applications is characterised by a high degree of uncertainty and by knowledge that runs the risk of getting outdated in a short space of time, the NBC highlights some of the requirements for the genetics centres and the laboratories carrying out such tests. It stresses that the uncertain demarcation of the line between research and its clinical applications must never let one lose sight of the fact that the diagnostic tests are primarily aimed at giving a diagnosis to the patient, whose needs must remain at the centre of the investigation, and thus recommends that the patient/sample are included in a research project only when the diagnostic investigation has been concluded (either positively or negatively).

Furthermore, it recommends that the traditional distinction is made between adults and minors in clinical investigation and research and that the 'best interest' of the subject, not yet able to give their own consent, is placed under a particularly careful assessment. It is also recommended that, upon coming of age, the minor is contacted and able to choose to give/not give their consent to the further conservation of their samples and data (as already highlighted in the Opinion *Paediatric biobanks*).

As far as concerns the question of the returning of information to the donors of biological samples for research purposes, the NBC considers that, in the case of research foreseeing the gathering of large samples, it is unrealistic to contact the donors to update them on the results, which to date would hardly have any clinical significance of single interest. On the other hand, it considers that if requested it is morally dutiful to guarantee the return of the results of clinical relevance (incidental findings included) to patients with rare diseases and still without a certain diagnosis, always leaving the possibility of opting only to know some types of information to the individual.

Lastly the NBC stresses that the central role played by genetics and genomics in the healthcare panorama makes it increasingly urgent to rethink the training of the professional figures committed to this field of medicine and, at the same time, the organisation (starting from the school) of initiatives at various institutional levels aimed at citizens, in order to foster the acquisition of

the necessary knowledge, which equally includes bioethical knowledge, so as to actively and critically tackle these transformations.

The Working group was coordinated by Profs. Monica Toraldo di Francia and Bruno Dallapiccola, who prepared the draft of the document.

The following took part in the drafting of the document and in particular Profs.: Silvio Garattini, Carlo Petrini and, in the working group discussion, Salvatore Amato, Carlo Casonato, Rosaria Conte, Lorenzo d'Avack, Antonio Da Re, Demetrio Neri, Laura Palazzani, Grazia Zuffa.

The group met for the first time on 19 June 2014 and, after various meetings, the Opinion was debated in the plenary session on 26 February 2016.

The expert advice of Prof. Dallapiccola was given on "The point on personalised medicine (genomic analyses of complex illnesses)" and by Prof. Alberto Piazza.

The document was approved by the members present, Profs.: Amato, Battaglia, Canestrari, Caporale, d'Avack, Da Re, De Curtis, Di Segni, Flamigni, Frati, Gensabella, Morresi, Neri, Nicolussi, Sargiacomo, Scaraffia, Toraldo Di Francia, Zuffa.

The members without the right to vote expressed themselves in favour Drs.: Benato, Bernasconi, Conte, Petrini.

Profs. Caltagirone, Casonato, D'Agostino, Dallapiccola, Garattini, Palamara, Palazzani, Proietti endorsed the Opinion at a later date.

Lorenzo d'Avack

Preamble

Over the years the NBC has dedicated numerous documents to the theoretical evolution and clinical repercussions of human genetics; even though maintaining their bioethical validity today, these documents can be interpreted as successive updates of issues and problems inherent to the rapid developments of this discipline. Some of the titles include: *Bioethical guidelines for genetic testing* (1999), *From pharmacogenetics to pharmacogenomics* (2006); *Genetic testing and insurance* (2008)[1]; *Collection of biological samples for research purposes: informed consent (*2009*)*[2]*, Paediatric biobanks* (2014). In 2010, the document *Genetic susceptibility testing and personalised medicine*[3] was published, on the applications of genetics to the safeguarding of health in multifactorial disorders and the first steps of the so-called 'personalised medicine' (today the term 'precision medicine' - PM is preferred), able to '*directly recognise the individual variability in the relationship between genetic structure, environmental factors, lifestyle and the individual's biographical history*'. The NBC deemed it appropriate to recall the contents of this detailed and structured document, which represent the background framework of the new Opinion. The 2010 document is divided into two sections, dedicated respectively to the *Scientific aspects of the susceptibility tests in complex adult diseases and the concept of personalised medicine* and the *Standards for good clinical practice, genetic counselling, deontological aspects, of bioethics and forensic medicine*, integrated by conclusions and bioethical recommendations.

In the text a number of previously dealt with subjects are taken up once again and examined in detail, like for example those regarding the distinction of the various types of genetic tests, the legitimacy and possible limitations of the right not to know, the risk that, beyond statements of principle, discriminatory and/or stigmatising behaviour can be manifested on the basis of assessments related to the individual genetic profile and instances of selection at work, school, etc. Nevertheless, the aim was to go beyond this and offer a broad reflection '*on the actual present, as well as prospective, value of the evolution of genetic research in the medical-healthcare field*' and on its related bioethical problems, focussing in particular on two interdependent sectors at the centre of a number of expectations. The first is that of the studies on the influences of hereditary traits in the most common multifactorial disorders (*'owing to the interaction between the additive effect of many genes and the environment'*), a sector which has given rise to the rapid proliferation on the market of the offer of predictive and susceptibility tests, of which the scientific validity is often not controlled, let alone the clinical one. Even then it was highlighted how the growing tendency to encourage the commercialisation of this typology of investigation without medical prescription and an adequate

[1] The document was drafted by the Joint Group, made up of the NBC and the National Committee for Biosafety, Biotechnology and Life Sciences (CNBBSV).

[2] Opinion edited by the Joint Group. A standardised format of a form for a flexible informed consent is attached (specific consent, partially limited, multi-option, broad), for the collection, preservation and use of cells and tissues in biological banks.

[3] This Opinion was also drafted by the Joint Group. The three Joint Group Opinions, along with three commentaries and Preface by Adriano Bompiani, have now been put together in a book by M. Galletti and M. Toraldo di Francia (edited by), *Bioetica e genetica. Indagini cliniche e biobanche tra etica, politica e società,* Franco Angeli, Roma 2013.

genetic counselling was a cause for great concern. Moreover, this took place by resorting to forms of misleading advertising and undue pressure on citizens-consumers, unaware of the dubious scientific and clinical validity of information to be obtained with this 'freedom' of initiative, just as also the possible negative medical and non-medical consequences that could arise from this. The second sector of interest is in the research of pharmacogenetics and pharmacogenomics, which instead investigate the '*modalities of response to drugs at the level of the molecular structure of cells and tissues*' with the aim of developing tests to increase the efficacy of treatments and reduce the risk of adverse effects of a specific drug for a specific individual (the '*precision medicine*' – PM sector).

Instead, the second section addresses the role played by genetic counselling, along with an in-depth examination of the related bioethical issues – from those pertaining to informed consent to those of the protection of confidentiality and privacy and the relationship between the person undergoing the testing and their family etc. – also in view of the future growing development of clinical genetics and PM.

In this document the NBC had also foreseen that the rapid evolution of second generation genomic sequencing technologies (the so-called *Next Generation Sequencing*, NGS) would have transformed and speeded up the research and diagnosis of many disorders; in the meantime these forecasts have for the most part materialised, to such an extent as to justify the affirmation of being before a real "*genomic tsunami"*.

1. New genome sequencing technologies: WES and WGS

While in the past only single segments of DNA could be analysed, the new techniques make it possible to decrypt the whole exome (*Whole Exome Sequencing*, WES), or the whole set of exomes, about 1% of the genome, corresponding to the DNA transcribed into mature RNA, or even the whole genome (*Whole Genome Sequencing*, WGS), including a person's coding and non-coding sequences. All this can be done in time and with costs that are 1,000,000 times lower with respect to those necessary in 2000, when the first sequencing of the human genome was made public.

This progress has facilitated the access to genomic information and has brought about a significant increase in the use of new technology platforms both in clinical contexts (for example, diagnostics, pharmacogenetics, in screening) and in research. Commercial pressure then led numerous groups to propose the *Genome Wide Analysis* (GWA), or the analysis of specific portions of the genome, in the prediction of the individual susceptibility to getting a disease and various websites offer different genetic tests (susceptibility to common illnesses, personalised diet, ability in sports, choice of partner, etc.) directly to consumers (so-called "*Direct to consumer Genetic Testing"* - DCT)[4].

A fundamental feature of the ongoing technological revolution is the promise and, in some cases, the actual possibility of defining heritability (that is,

[4] On these aspects of DCT, see the Opinion by the Joint Group, *Genetic susceptibility testing and personalised medicine,* cit.

the hereditary component), or part of the heritability of diseases and complex traits from a new perspective and, at the same time, to come closer to the objective of 'personalising' medicine and therapies. The NGS techniques have ascertained that the genome of each person differs from those of others by almost 4 million base pairs (for the most part these are polymorphisms, common genetic variations shared by at least 1% of the population, but often by many more) and has about 1500 'unique' bases, not present in the human genome reference maps. These variations are at the basis of inter-individual differences and give the foundation to the predictive tests, which measure the susceptibility and resistance of each person to common diseases.

The association between specific polymorphisms and diseases or complex traits, and hence their value in terms of susceptibility and impact on a certain phenotype, is established by means of the analysis of a great number of samples (thousands/tens of thousands) of subjects carrying a disease and unaffected controls. These studies make it possible to highlight the polymorphisms present in a significantly greater or smaller percentage of people affected, with respect to the controls, in support of a random association with the disease in question. As they are complex phenotypes, deriving from the additive effect of the genetically determined susceptibility and the environment, the predictive significance of the single polymorphisms is low (average additional risk 1.1-1.5). The 2,000 or more studies that have been carried out since 2005 on over 250 complex diseases/traits have made it possible to identify over 12,000 polymorphisms of susceptibility/resistance[5]. Nevertheless, apart from a few exceptions, the average hereditability decrypted for the single diseases is low and does not go over 15%. Furthermore, given that the frequency of polymorphisms in the various populations can be highly variable (with differences even in the range of 25%!), the transferal of research results in clinical practice should be very carefully considered insofar as the prediction of risks cannot disregard the knowledge of the frequency of the polymorphisms investigated in the population from which the person being offered the test originates.[6]

The impressive technological development and the consequent easy access to genomic analyses does not make it possible to make forecasts beyond a time span of 3-5 years, but justifies the question as to what the impact of large scale access to predictive tests will be.

With regard to the present we stress that:

a. at the moment it is premature to constructively use most of these results in a translational way and to offer an ad hoc genetic counselling. The biological bases of only a part of the genetic diseases are known and only a small part of

[5] D. Welter , J. MacArthur, J. Morales, T. Burdett, P. Hall, H. Junkins, A. Klemm, P. Flicek, T.A. Manolio, L. Hindorff, H. Parkinson*, The NHGRI GWAS Catalog, a curated resource of SNP-trait associations,* "Nucleic Acids Research"*,* 2014, January, 42 (Database issue).

[6] T.A. Manolio*, Genomewide association studies and assessment of the risk of disease, "*The New England Journal of Medicine*",* 2010, July 8, 363 (2), pp. 166-176. The fact that the differences in the frequency of polymorphisms can depend on individual ethnic appurtenance is highlighted in many articles and documents, which stress how most of the known pathogenic mutations have been discovered in the Caucasian populations.

the heritability of the complex ones; furthermore, the complex mechanisms whereby the environment modulates the action of the genome are only known in a piecemeal fashion.

b. the follow-up of the persons undergoing GWA with a DTC approach showed that the behaviour adopted following the giving of the test results is not significantly different from the behaviour that could have been adopted without undergoing a costly genomic investigation, insofar as choices oriented solely by common sense[7].

c. from the epistemological point of view, human genetics has modified its reference paradigms over the last years. It has in fact become clear that numerous products interpose between the genotype and phenotype, which share the '-omic' suffix, currently used to indicate a wide number of disciplines or biomolecular derivatives (including transcriptome, proteome, metabolome), which identify the different functional expressions of genes[8]. These products are not static but change significantly during life, in a different way in the various organs and apparatuses. Their totality defines the integrome, the ideally most appropriate parameter to describe the individual genomic or post-genomic profile[9].

Moreover, today it is considered that these continuous changes are for the most part dependent on the individual exposome or, that is, on the lifestyles and the environment in which we develop, grow and live, including the trillions of bacteria present in our organism and, among these, in particular, the symbiotic microorganisms of the intestine (microbiota), which from birth play an important role in the modulation of the immune system of the host and the genome[10]. This not only means that a person cannot be defined uniquely on the basis of the genomic sequence inherited at the moment of conception (the old idea of genetic determinism), but also that post-genomic medicine is overtaking the traditional 'reductionist' approach to move towards a holistic vision and one of 'systems medicine', which in an interdisciplinary way looks at the human body as an integrated totality, which incorporates complex genomic interactions, both environmental and behavioural[11].

The convergence of systematic approaches to diseases – including the new diagnostic instruments and 'omic' investigations, together with the new mathematical and computational tools – is destined to revolutionise the traditional paradigm of medicine with regard to the patient and in the next years

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[7] D.J. Kaufman, J.M. Bollinger, R.L. Dvoskin, J.A. Scott, *Risky business: risk perception and the use of medical services among customers of DTC personal genetic testing, "*The Journal of Genetic Counseling," 2012, June 21, (3), pp. 413-422*;* G. Remuzzi, *Così ho fatto la mappa del DNA e la mia vita è cambiata, "*Corriere della Sera", 28 luglio 2014.

[8] M. Baker, *The 'omes puzzle, "*Nature*",* 2013, 494, pp. 416-419.

[9] R. Chen, G.I. Mias, J. Li-Pook-Than, L. Jiang, H.Y. Lam, R. Chen, E. Miriami, K.J. Karczewski, M. Hariharan, F.E. Dewey, Y. Cheng, M.J. Clark, H. Im, L. Habegger, S. Balasubramanian, M. O'Huallachain, J.T. Dudley, S. Hillenmeyer, R. Haraksingh, D. Sharon, G. Euskirchen, P. Lacroute, K. Bettinger, A.P. Boyle, M. Kasowski, F. Grubert, S. Seki, M. Garcia, M. Whirl-Carrillo, M. Gallardo, M.A. Blasco, P.L. Greenberg, P. Snyder, T.E. Klein, R.B. Altman, A.J. Butte, E.A. Ashley, M. Gerstein, K.C. Nadeau, H. Tang, M. Snyder*, Personal omics profiling reveals dynamic molecular and medical phenotypes,* "Cell", 2012, 16, 148 (6), pp. 1293-1307.

[10] L. Putignani, F. Del Chierico, A. Petrucca, P. Vernocchi, B. Dallapiccola, *The human gut microbiota: a dynamic interplay with the host from birth to senescence settled during childhood,* "Pediatric Research*",* 2014, July, 76 (1), pp. 2-10.

[11] T. Kamada, *System biomedicine: a new paradigm in biomedical engineering, "*Frontiers of medical and biological engineering", 1992, 4 (1), pp. 1-2.

to go on to develop a Preventive, Predictive, Personalised, Participatory medicine (the so-called '4P medicine')[12].

2. New questions: NGS and Incidental Findings – IF

The speed in the advance of technological development applied to the analyses of the human genome has raised a series of new questions of a bioethical nature. In particular, with regard to the managing of genetic and genomic analyses, there has been wide debate on how to re-intervene on the existing normative frameworks regulating research and its clinical applications and it has been asked if and to what extent, it is appropriate to question a number of consolidated principles.

The need for new shared guidelines – at local, national and international levels – for the management of the challenges of this delicate stage of transition of the human genome is a strongly felt need also because the use of WES and WGS technologies, which generate a huge amount of data of potential clinical interest (which require complex bioinformatics analyses for their interpretation), weakens or even erases some traditional distinctions:

1) between research and clinical investigation, insofar as the two dimensions seem to be increasingly interwoven, and at the same time the problem of how to store and manage the growing amount of information that is becoming available[13];
2) between diagnostic tests and screening – understood as medical tests offered to asymptomatic persons and for whom there are no clinical indications such as to make them necessary – since the use of WES and WGS in the clinical context in principle generates a range of unforeseen information and/or uncorrelated with the original diagnostic query[14].

Whenever considering the great number of recommendations which have been drafted in recent years by the scientific organisations to regulate the management of NGS techniques, both in clinical applications and in research, it can be seen that in these documents the concern is always expressed of how to maximise the potential benefits and minimise the potential damage (in terms of false positives, the protection of confidentiality and privacy of information[15], etc.) respecting the dignity and autonomy of the people involved, but also – at least in many recommendations – their right to an open future, to the extent that

[12] L. Hood, M. Flores*, A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory,* "New Biotechnology", 2012, September 15; 29 (6), pp. 613-624*;* M. Flores, G. Glusman, K. Brogaard, N.D. Price, L. Hood, *P4 medicine: how systems medicine will transform the healthcare sector and society,* "Per Med.", 2013, 10 (6), pp. 565-576.

[13] C.G. van El, M.C. Cornel, P. Borry, R.J. Hastings, F. Fellmann, S.V. Hodgson, H.C. Howard, A. Cambon-Thomsen, B.M. Knoppers, H. Meijers-Heijboer, H. Scheffer, L. Tranebjaerg, W. Dondorp, G.M. de Wert, ESHG Public and Professional Policy Committee, *Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics,* "European Journal of Human Genetics", 2013, June, 21, Suppl. 1: S1-5.

[14] B.M. Knoppers, *Introduction From the Right to Know to the Right Not to Know,* "The Journal of Law, Medicine & Ethics", Spring 2014, Special Issue: Symposium: The Right Not to Know, Vol. 42, pp. 6-10.

[15] On the difficulties met by the protection of privacy in the age of NGS testing and 'big data', see in particular S.S. Shringarpure and C.D. Bustamante, *Privacy Risks from Genomic Data-Sharing Beacons.* "American Journal of Human Genetics", 2015, November 5, 97, pp. 1-18.

is considered most appropriate by each of them. While the shared objective [16] is to speed up the progress of 'precision medicine' and the development of the so-called '4P' medicine as far as possible, the risk feared by many is that a growing recourse to these methodologies in genetic diagnostics might lead to the automatic inclusion of patients in protocols of fact-finding studies, subordinating their individual interests to the research goals of their doctors. Thus, for example, the identification of a new variant of potential importance for the progress of scientific knowledge of a specific pathology, and therefore of great interest for research, could at the time be irrelevant for clinical ends; this would not only be difficult to explain to the patient, but could even be a cause of stress and anxiety to them and their family or also be responsible for provisions and inappropriate medical management[17]. Under this profile there seems to be widespread consensus on the need to proceed cautiously as far concerns the introduction of the new genomic technologies into medical practice and on the rejection, in principle, of every simplistic application of the so-called 'technological imperative' (everything must be offered that every technological advancement makes viable).

The hope mostly expressed by specialised literature is that an active exchange of experiences might be established between the geneticists that use WES and WGS, with clinical and/or research ends, in order to draw up shared rules that set down, case by case, the gradualness in the use of NGS techniques, as well as which genomic information can be extracted and when it must be documented, filed, shared and for how long. In parallel, there is a hope for the construction of common normative frameworks that:

a. redefine the different stages and contents of genetic counselling in an appropriate manner for the new challenges together with the procedures for informed consent, differentiating research from clinical applications, and likewise for the management in both dimensions of the so-called 'incidental findings'- IF and the variants whose clinical implications are not yet certain (*variants of unknown significance* - VUS);

b. make it possible to come to a shared definition of what is meant by 'clinical utility', as a criterion legitimating the request for genetic testing or genomic analysis (definition on which there are a number of differing opinions).

With respect to point (b), the problem has long been debated, initially starting from the question of the guiding criteria to be applied in the offer of neonatal screening tests, to then also affect the guidelines for genetic and genomic analyses[18]. From this exchange of opinions a persistent contrast between two main concepts comes to the fore. One group considers that the classical criteria still hold and according to which the clinical utility of an investigation should be focalised on the identification of conditions for which efficient treatment or preventive measures aimed at reducing the morbidity and mortality are readily available. On the other hand, the other group proposes to extend its meaning,

[16] On the announcement made by President Obama of huge financing for a new research initiative aimed at speeding up the progress towards the era of *precision-personalized medicine* see: F.S. Collins and H. Varmus, *A New Initiative on Precision Medicine,* "The New England Journal of Medicine*",* 2015, February, p. 26.

[17] C.G. van El et al., *Whole-genome sequencing in health care Recommendations of the European Society of Human Genetics,* cit.

[18] *Id*.

under the profile of the contents and interests to be taken into consideration. As far as the contents are concerned, the conditions are included that do not require immediate medical intervention, or for which efficient treatment is not available, or which are not clearly pathological. With regard to the possible benefits, the assessment is also extended to the interests of the family circle of the subject in question. In this second perspective, all the so-called 'actionable'[19] information, or rather the information which prefigures the possibility of a decision-making intervention on the part of the subject and their family (reproductive decisions, planning of life choices, insurance plans, etc.) come into the list of information of clinical utility and, consequently, to be communicated.

Looking more closely at the questions raised by the latest developments of genetic-genomic diagnostics, the debate has focused above all on the pros and cons in both research and clinical investigation of giving the persons directly concerned the so-called IF, that the WES and WGS inevitably generate and which can be important for health and/or for reproductive choices (the IF and VUS can moreover play a crucial role in the understanding of the genotype-phenotype correlations[20]), as well as on the exchange of reasons given in support of the different standpoints.

The *Presidential Commission for the Study of Bioethical Issues* of the United States, which had already in part dealt with the subject in the document *"Privacy and Progress in Whole Genome Sequencing"*[21] (with particular reference to wide scale genetic sequencing), dedicated its detailed report to IF "*Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts*"[22]. In this document the IF are defined as "results that are outside the original purpose for which a test or procedure was performed". The Commission divides the IF into "*anticipatable"* and *"unanticipatable*". The former are those in which the possible association with a test or procedure is known. The latter are the IF that cannot be foreseen on the basis of the knowledge at hand. Furthermore, the Commission distinguishes between "*primary*", "*secondary*" and "*discovery findings*". "*Primary findings*" refer to a result that is actively sought, using a test or procedure designed to find such result.

The "*secondary findings*" refer to the results that are actively sought by a professional, but which are not the "*primary target*". The "*discovery findings*" refer to the results of wide tests, aimed at detecting any potentially interesting

[19] G.M. Christenhusz, *To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts,* "European Journal of Human Genetics", 2013, 21, pp. 248-255.

[20] See L.G. Biesecker, *Incidental Variants Are Critical for Genomics,* "The American Journal of Human Genetics", 2013, May 2, 92, pp. 648-651.

[21] Presidential Commission for the Study of Bioethical Issues, *Privacy and Progress in Whole Genome Sequencing,* 2012*,* www.bioethics.gov/cms/sites/default/files/Privacy-and-Progress_PCSBI.pdf.

[22] Presidential Commission for the Study of Bioethical Issues, *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts,* 2013.

data. The recommendations formulated by the Commission differ according to the IF category.[23]

With respect to this aspect of the debate, while most agree in maintaining that all the IF of proven 'clinical utility' must be communicated – meant in the sense of availability of treatment or efficient prevention measures – on the other hand opinions differ in specialist literature, discussion forums and in reviews, concerning the advisableness of communicating the IF of uncertain clinical significance (at the moment most of the IF), or those predictive of untreatable pathologies, or of the risk of a disease that is not quantifiable at individual level.

The different concepts also affect the way of thinking-rethinking genetic counselling, which must prepare patients, family and practitioners both to deal with more or less high levels of uncertainty and the processes and limitations of informed consent. In fact, not all of them are in favour of leaving patients enrolled in a research study, or who need a genomic investigation, more than one option to know/not know the IF discovered during the investigation (for example, no knowledge; qualified knowledge, or only the information of clinical interest liable to intervention, including or not including the information important for reproduction choices; knowledge of the variants of uncertain clinical significance, etc.). In reality, there are thus considerable differences regarding the identification of the most suitable modalities to protect patients and subjects enrolled in studies.

Even considering the European context alone, with regard to the use of NGS techniques in clinical diagnosis, a general agreement has not yet been reached on the question of documentation, reporting and communication of IF and the unclassified variants; more specifically: on the rules that genetic diagnosis laboratories should adopt, the modalities of storage-filing-sharing of the data produced from these analyses with other laboratories and on the actual possibility of their future re-interrogation[24]. As far as the research is concerned, the debate is made even more complex by the scepticism of many researchers about the concrete possibility of guaranteeing a return of information to those who donate biological samples, progressively as new data are made available on genetic variants that are potentially important for health. The vast amount of data generated and the possible, or probable, loss of contact with the original donors in fact seems to make the respect for the 'right' to be informed hardly realistic, should there be an explicit request, unless new modalities to maintain relations and communication by websites, social forum etc. are identified.

[23] Even though recognising that the expression *Incidental Finding* is not always the most appropriate, the NBC continues to use it in this document because it is used internationally. For example: J.K. Hehir-Kwa, M. Claustres, R. Hastings, C. van Ravenswaaij-Arts, G. Christenhusz, M. Genuardi, B. Melegh, A. Cambon-Thomsen, P. Patsalis Vermeesch, M.C. Cornel, B. Searle, A. Palotie, E. Capoluongo, B. Peterlin, X. Estivill and P.N. Robinson, Meeting Report, *Towards a European consensus for reporting incidental findings during clinical NGS testing,* "European Journal of Human Genetics*",* 2015, 23, pp. 1601–1606; Hellenic National Bioethics Commission, *Incidental Findings in Research and Clinical Practice,* 26 June 2015. In the Meeting Report it is stressed that the use of the expression *incidental findings* includes (i) unexpected positive findings, but also (ii) the intentional search for pathogenic variants not associated with the primary diagnostic query. Nevertheless, it is considered that the use of a different term, for example, 'unexpected' or 'secondary' or 'unsolicited' findings, is just as problematic and therefore it is advised to keep to the most common use of '*incidental findings'*.

[24] Cfr. Meeting Report, *Towards a European consensus,* cit.

Given the rapid progress of genetic and genomic research, even the *International Bioethics Committee (IBC)* of UNESCO[25] felt the need to update the previous documents on the genome and human rights, elaborating its new considerations in which the ethical issues deriving from the most recent advances, both in genetic diagnostics and the emerging gene-editing techniques, are listed and tackled. In the latter document, the IBC wishes to highlight how at present it is the very lack of a widespread ethical sensitivity, together with the inexistence of a framework of shared rules at international level, that risks producing harmful effects in terms of protection of fundamental human rights, increasingly marked inequalities in life and health expectations, new dangers of discrimination and/or stigmatisation of persons and/or specific groups.

a) Aspects of the bioethical debate on IF

A catalysing role of the debate on some of the above mentioned subjects was carried out by the publication of the *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing*, drafted in 2013 by the *Working Group* of the *American College of Medical Genetics and Genomics (ACMG)*[26]*,* which questioned the guidelines on the offer of genetic testing in medicine. According to the authors, in the age of the "*genome wide*" (GWA) analyses, many old rules and distinctions would no longer have any justification, as they are just a hindrance to the development of knowledge and a restraint to the translational use of new acquisitions. With regard to this, the *Recommendations* identify three main critical targets:

1) First of all, the thesis of the non-comparability of genetic information to other clinical data is rejected, or the thesis of the so-called genetic 'exceptionalism', conferring to this category of personal information a special legal status and a particular safeguard in terms of *privacy*.[27] According to the Working group, when a genomic analysis is carried out an attempt should be made to communicate all the information of potential clinical interest, whether correlated or not to the primary diagnostic question, just as happens when, for example, a patient complains of symptoms in the digestive system, the doctor does not just examine that system but extends the examination to the heart and lungs to try and find the evidence of a complex illness, or to discover other symptoms of the disease.

2) Secondly - 'genetic exceptionalism' having been rejected – the subjects who undergo a WGA, upon specific medical advice, are denied the possibility to exercise the 'right' to not know some secondary results (IF), independently of

[25] UNESCO – International Bioethics Committee*, Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights,* 2 October 2015.

[26] R.C. Green, J.S. Berg and W.W. Grody et al. for the American College of Medical Genetics and Genomics, *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing,* "Genetics in Medicine*",* 2013, 15, no. 7, pp. 565-574.

[27] Genetic 'exceptionalism', recognised by many supranational documents, and not without contestations, is justified on the basis of the peculiar nature of these 'very sensitive' data, (i) which are structurally shared with other subjects belonging to the same biological group and (ii) that '*make it possible to know in advance a number of aspects concerning one's biological future, in terms whether it be of greater susceptibility with respect to the average, to having certain diseases (or also resistance to the same), or predestination to getting a certain disorder or an early death'*, see Opinion by the Joint Group, *Genetic testing and insurance,* cit.

their preferences and clinical condition. The drafters of the document recognise that this recommendation is in conflict with the ethical and juridical norms that safeguard the patient's autonomy, but consider that the doctors and laboratory staff, have a more cogent 'fiduciary' duty, which is one of preventing any potential harm (principle of beneficence) and, for this reason, to always give patients the IF of potential interest for their health, even against their will.
3) Thirdly, in relation to the rules to be applied in the carrying out of genomic analyses, the distinction between minors and adults is rejected. In stressing the need to always communicate the IF, at least concerning the analysis of a given group of genes, even if they are predictive of genetic diseases with late-onset and incurable and/or preventable, the Working group maintains that this rule should hold also in case where the investigation concerns new born babies, children or adolescents. Once again it can be seen that a similar indication is in clear contrast with the most accredited guidelines on the subject, which recommend not to subject minors to predictive genetic testing at the outset of adult life, which are neither preventable nor sensitive to efficacious treatment. This recommendation is defended with the justification that, in the balance between the possible benefit for the parents deriving from the knowledge of their genetic risk and the potential harm that could be done to the minor with the questioning of their future autonomy and right to an open future, at present the first aspect prevails over the second.

In short, the ACMG Working group recommends that, when a WGA is prescribed with a specific clinical suspicion, a series of conditions/genes/variants are always analysed (the Table attached to the recommendations lists 56 genes associated with the risk of various diseases; this list is subject to yearly updating); the positive tests must then be communicated to the doctor prescribing the testing and he or her in turn must inform the patient, without leaving him or her the faculty to opt for non-knowledge of the results not correlated to the primary clinical suspicion or to opt to know only some. Despite admitting the lack of significant data on the clinical utility of these recommendations, the drafters support their fairness, relying on the argument of the future advantages to be derived from the acquisition of new knowledge, through the gathering of empirical data on the penetrance of a series of variants of interest, as well as evidence useful for improving the analysis of the cost/benefit relationship.

Besides the acceptability or not of the tests carried out, these recommendations have had the merit of stimulating a huge structured debate on the ethical legitimation of the 'right not to know' in a genetic context, during which misunderstandings and misinterpretations arose which have always existed in the bioethical debate on this controversial right and its possible theoretical foundations. The same ACMG *Board of Directors*, following a broad consultation of its members on the opinions, was led to review its own standpoints, recognising patients who undergo WES or GWA the possibility, during the pre-test phase of the counselling, to allow or not allow the extension of the investigation to the genes included on the list not correlated to the original

diagnostic suspicion (excluding the option to choose only a subgroup of clinically 'actionable' genes)[28].

b) Conceptual misinterpretations: 'self-determination', 'autonomy', '*privacy*'

In this clarification process, an important part was played by the Symposium *From the Right to Know to the Right Not to Know,*[29] held in Canada in the spring of 2014 – with the participation of numerous scientists, jurists and moral philosophers – who contributed to clarifying the assumptions of the right not to know from a conceptual point of view. The discussion during the Symposium and what followed on from it was focussed on three main issues:

i. the first, the more theoretical one, concerns the legitimation modalities of the 'right' to not receive personal information regarding one's health, genetic-genomic information included. It soon became apparent how the diverging ethical-philosophical interpretations of the concept of 'autonomy' lead to basing arguments both in favour and against the recognition of the 'moral' right not to know (RNTK) on contrasting ethical and juridical principles.

ii. the second question regards the possibility or not of envisaging a moral duty to undergo tests, when it is presumed that they may be relevant not only for one's life choices, reproductive ones included, but also those of one's blood relatives. With its evident sociological implications this second profile of the debate contributed to defining, not without differing opinions and more or less knowingly, a new figure of 'ideal citizen': an autonomous, careful, responsible subject, who formulates his or her own life strategy in a calculated way, with choices that look to the future in terms of optimisation of management of their own biological 'risk' and that of their next of kin, availing of biomedical knowledge, as a resource for the planning of their existence[30].

iii. the third query concerns researchers and their possible obligation to guarantee, also for the future, a return of information of clinical utility to the participants enrolled in genetic and genomic testing.

While the debate is still ongoing on points (ii.) and (iii.), as far as concerns point (i.) a number of important conceptual clarifications have been made, which should be briefly summarised insofar as useful to outline more precisely what is at stake in the bioethical debate on IF.

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[28] See American College of Medical and Genomics, *Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results*, Bethesda, 2014, April 1, https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf

[29] *From the Right to Know to the Right Not to Know,* "Journal of Law, Medicine & Ethics", cit., pp.1-6.

[30] See N. Rose, *The Politics of Life Itself. Biomedicine, Power and Subjectivity in the Twenty-First Century,* Princeton University Press, Princeton 2007. Also the last UNESCO document on the subject highlights how the possibility to know one's own genomic make up can give rise to the social expectation that persons plan and live their lives in accordance with this knowledge. This expectation could not only make people lose sight of the importance for health of the many social determinants affecting it, but also lead to discriminate and stigmatise those who do not adopt "*a health-promoting lifestyle*"; see *Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights,* cit.

It must be first of all recalled that until 1977 the supranational and international documents of normative importance did not mention the possibility of guaranteeing a right not to know in healthcare, insofar as the emphasis had moved to the individual right to be informed. Only in 1997 did the RNTK, characterised as an aspect of personal autonomy, find its first formal recognition – which was followed by many more in the *Universal Declaration on the Human Genome and Human Rights* UNESCO (art.5) and, in the same year, in the *Oviedo Convention on Human Rights and Biomedicine* (art.10). Nevertheless, the question of the plausibility of the RNTK in the bioethical debate has continued to be a controversial matter, owing to the persistent lack of agreement on the ethical-philosophical meaning of the concept of 'autonomy' and the ensuing rights and/or interests to be safeguarded[31].

There are three main interpretations of this concept, which in turn envisage different ideals of what can be meant by 'autonomous decision' and different, sometimes conflicting, approaches to their normative importance.

For the first ideal, what has value and is worthy of protection, is the non-interference by others in the most personal and inmost decisions. In this case autonomy coincides with the personal liberty of the competent adult subject to decide on their own life and, therefore, requires a policy that might guarantee the corresponding rights, including that of refusing to receive information on one's own health.

The second much more demanding interpretation interprets the concept as an ideal that requires the competent subject, insofar as moral agent, to be in control of the circumstances of their own existence. For this concept people have the right and duty to know as much information as possible about their own state of health, genetic make-up included, to be able to exercise 'self-governance' taking rationally controlled decisions[32], or that is, based on all the relevant information that can be obtained. This excludes the possibility *a priori* of morally establishing the claim to remain in ignorance.

A third concept of the notion, often disregarded and opposed to the previously mentioned one, instead connects autonomy to an ideal of 'authenticity'. From a philosophical perspective, this standpoint found its most respected supporter in the 70s in the person of Hans Jonas. With the rapid advance in biomedical technologies which seemed to question the '*right to every human life to find its own way and to be a surprise for itself*', Jonas had already envisaged the emergence of a new moral right, that is, a right to the ignorance of one's own future, which in certain situations (for example, in the case of predictive information on late-onset non-preventable and untreatable

[31] In particular see the essays by: G. Laurie, *Recognizing the Right Not to Know: Conceptual, Professional, and Legal Implications*, cit. pp. 53-63*;* G. Helgesson, *Autonomy, the Right Not to Know, and the Right to Know Personal Research Results: What Rights Are There, and Who Should Decide about Exceptions?* in *From the Right to Know to the Right Not to Know,* cit.

[32] J. Harris and K. Keywood, *Ignorance, Information and Autonomy,* "Theoretical Medicine*",* 2001, 22, 5, pp. 415-436.

genetic diseases), can be presented as a precondition of the free construction and definition of self-identity.[33]

While the second interpretation is incompatible with the recognition of the RNTK, instead for the other two such right finds a foundation, at least as a 'prima facie' right (or liable to exceptions in particular circumstances), in the one case in the negative freedom of the person and in the other in the 'existential' freedom of self-determination according to one's values and lifetime plans.
Nevertheless, if one passes from the philosophical-moral level to the factual one of the concrete dilemmas that doctors and doctors-researchers can be faced with when they find themselves before IF, the above mentioned do not help to resolve the question of the decision to be taken should an explicit expression of will by those directly concerned be lacking to be or not be informed.[34] In these cases some consider that a reconceptualization of the interest to not know is more suitable as a question deriving from the interest in the respect for privacy[35], understood as 'separateness' of the 'private' personal sphere – including the very individual psyche - not accessible to others if not for good reasons. In this perspective it can therefore be maintained that the communication of unsolicited personal information, regarding one's own genetic makeup can constitute, more than a violation of autonomy, an invasion of the individual psychic sphere.

In conclusion it can be said that the interest and/or right not to know must be safeguarded as much as possible, even though it is never absolute insofar as it can come across limitations, in factual circumstances, for reasons that surpass it and which must therefore be convincingly argued each time. A certain degree of discretion can never be completely avoided since it ultimately lies with the responsibility of the doctors and doctors-researchers, with the help of other consultants, to decide on the 'exceptions', bearing in mind the relevance of the typology of information at stake.

Recommendations

Even though aware that this transition from basic knowledge to clinical applications is characterised by a high level of uncertainty and knowledge that risk being surpassed very rapidly, the NBC has formulated a number of recommendations.

1- For the tests based on NGS, the NBC recommends that:

i. the analysis is carried out only in accredited genetic diagnosis laboratories, which are subject to external quality control, perform an adequate number of analyses, are equipped with updated databases and IT instruments, able to guarantee the accuracy of the diagnoses and the interpretation of the results, and an organisation for the storing of all the data generated, including incidental findings (IF) and variants the clinical implications of which are not yet

[33] On the concept of the "free formation of self" in relation to the "right to ignorance", see the Joint Group, *Genetic testing and insurance,* cit. and *Genetic susceptibility testing and personalised medicine,* cit.
[34] For example in the case of a diagnosis made with NGS on a biological sample of a dead subject and whose result can, nonetheless, have clinical relevance for blood relatives.
[35] Cfr. G. Laurie, *Recognizing the Right Not to Know: Conceptual, Professional and Legal Implications,* cit.

certain VUS – Variants of Uncertain Significance - considered time-dependent). The NBC expresses its hope that standard criteria might be shared and valid over all the national territory;

ii. the genetic centres share operational rules for the choice of molecular diagnosis techniques, which must be calibrated bearing in mind the specificity of the primary diagnostic query and the analysis of the variants identified. Should the WES analysis be negative, the centres must take the necessary measures for the preservation of the biological sample and the patient's data, so as to make them available for possible further analyses once new knowledge and data has been acquired;

iii. more room is reserved for the gathering of informed consent and pre- and post-test counselling, which must be an integral part of the analysis and be carried out by professionals with specific training, including psychological training[36];

iv. the patients undergoing counselling are informed preliminarily, in the pre-test genetic consultation, of the potential and the limitations of the analyses and the differences with respect to traditional tests, particularly with regard to the possibility of the analysis identifying IF of possible clinical outcome and VUS, as well as information on the possible biological blood relationships and information of pharmacogenetics interest and precision medicine. With regard to this and in line with what was proposed in a recent document of the Italian Society of Human Genetics (SIGU)[37], the NBC considers it useful for the patients undergoing consultation to be shown a number of significant examples of conditions whereby IF are more likely to be highlighted. Those undergoing testing must moreover be informed that the results of the analyses can have serious implications for their next of kin and that, in this case, it is appropriate and in some circumstances dutiful[38], to allow the latter to be informed with due caution and modalities;

v. in the obtaining of informed consent, the patient's right to self-determination be respected and therefore the choice to decide which results to know be left with the patient undergoing testing, once they have understood the difference between the various typologies of IF. The patient must be free to choose whether to refuse information on IF or to receive only the information relative to preventable or treatable pathologies, or again to also know the data regarding pathological conditions that at that moment are neither preventable

[36] Cfr. the paragraphs dedicated to outlining the modalities and contents of genetic consultation in the opinion by the Mixed Group, *Test genetici di suscettibilità e medicina personalizzata*, cit.

[37] SIGU-NGS Commission, *Il sequenziamento del DNA di nuova generazione: indicazioni per l'impiego clinico,* 2016, including attachments: *Indicazioni operative per la consulenza genetica associata ai test NGS, Informativa al consenso. Test genetico: "sequenziamento dell'esoma"; Foglio Informativo per l'analisi di regioni selezionate; Consenso Informato per Analisi di regioni selezionate; Schema risposta indagine NGS.* In this document it is specified that, in clinical diagnostics at the present time, WGS analysis is not considered owing to the high cost and difficulties of interpretation.

[38] For example in the case of information on serious diseases for which it is necessary to start preventive or therapeutic measures.

nor treatable[39]. In the pre-test counselling it is necessary to inform patients that in some cases the results of the tests many need further detailed examinations, for which the analysis of other members of the family might be required, to make it possible to study the 'segregation' of the variants identified[40]. Lastly it is necessary to ask the patient for a specific consent to be contacted in the future, should the need arise to do so;

vi. a relationship of collaboration and exchange of information be established between the laboratory, the geneticist and the other consultants having charge of the patient and that at the same time the collaboration is encouraged between the various diagnostic laboratories and genomic research. It lies with the geneticist who prescribed the testing to give the result, as he or she is acquainted with the patient's medical and family history, as well as with the choices taken down in the informed consent; in the post-test counselling he or she will be able to avail of the support of other professional figures, with psychological expertise too, who will help in the communication and planning of the patient's clinical management.

2- The NBC reiterates that the undefined demarcation of the boundary between research and its clinical applications must never make the geneticists and the other professionals lose sight of the fact that the diagnostic tests have the primary aim to give a diagnosis of the patient, whose needs must remain at the centre of the investigation; it therefore recommends that the patient/sample is included in a research project only after the course of diagnostic investigation has been concluded (either positively or negatively).

3- Furthermore, the NBC recommends that the traditional distinction between adults and minors be maintained in medicine and research alike, and that the 'best interest' of the subject not yet able to give their own consent should be particularly and carefully evaluated. For these cases it hopes that the genetic centres have specific standard rules, both for the modalities through which genetic counselling is carried out and for the communication of results (only those of proven clinical utility) to parents/legal representatives. It is also recommended that, upon coming of age, the minor is contacted once again and can chose whether to give/not give their consent to further preservation of their samples and data[41].

4- Regarding the question of the returning of information of biological samples for research to donors, the NBC considers that, in the case of research that foresees the gathering of large numbers of samples, it is unrealistic to contact the donors to update them on the results, which moreover, to date, would hardly have any clinical significance of individual interest. Therefore the NBC recommends that it is always specified in the informed consent form whether or not this possibility exists and, should it be so, that the choice of information that they desire to receive be left to the person concerned.

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[39] On the other hand, it is not appropriate to give the variants of uncertain significance, nor the susceptibility for the above mentioned reasons.

[40] SIGU-NGS Commission, *Il sequenziamento del DNA di nuova generazione,* cit.

[41] The subject has already been dealt with by the NBC in the 2014 Opinion on *Paediatric biobanks*.

5- On the other hand, the NBC considers that if requested it is morally dutiful to guarantee the return of the results of clinical importance (IF included) to the patients with rare diseases which are still without a certain diagnosis, who are part of study protocols and who donate their samples in the hope of advancing the knowledge of the causes of their illness, and thus recommends that this guarantee be maintained, always leaving the person concerned the possibility to opt to know only some types of information.

6- Lastly, the NBC stresses that the central role assumed by genetics and genomics in the healthcare panorama makes it increasingly urgent to rethink the training of professional figures working in healthcare together with the organisation, at various institutional levels (starting from school) of initiatives aimed at citizens, in order to promote the gaining of the necessary knowledge, including bioethical knowledge, to actively and critically tackle these transformations. In this sense the institutions must set up interventions aimed at countering misleading publicity, so that citizens are not the victims of the illusory and potentially harmful promises of many websites offering genetic and genomic testing directly to consumers.

Glossary

ACMG, *American College of Medical Genetics.*
Genetic counselling – A health service that provides information on genetic disorders relatively to their diagnosis, how the condition is inherited, the risks of occurrence or recurrence and the options for their control and prevention.
Person undergoing counselling – Person who receives genetic counselling
Pre-symptomatic diagnosis – Investigations aimed at ascertaining whether a person has inherited a gene-disorder before it is clinically manifested.
DTC, *Direct to consumer Genetic Testing - G*enetic testing refers to testing sold directly to consumers usually via private laboratories.
Hereditability – The hereditary component of a complex trait.
ESHG, *European Society of Human Genetics.*
Exome – Part of the genome formed by exons which represent the codifying portion of DNA. Even though constituting only 1% of the total amount of genetic material, it is made up of over 30 megabases (30 million bases) of DNA and is responsible for the building of our organism.
Expression – Variation in the degree of manifestation of a phenotype of a particular gene
Exposome - Totality of environmental factors to which an individual is exposed, lifestyle included.
Late onset age – Defines some phenotypes not present at birth, which are manifested in adulthood.
Phenotype – The appearance (physical, biochemical and physiological) of a person, which is influenced by the interaction of the genotype with the environment.
Gene Editing – gene or genome editing, which uses engineered nucleases, is a type of genetic engineering in which DNA is inserted, deleted or replaced in the genome of an organism using engineered nucleases, or "molecular scissors".

Genotype – Genetic makeup of a person.

GWA*, Genome Wide Analysis* – Analysis of the whole genome.

IBC, *International Bioethics Committee (IBC)* of the UNESCO.

IF, *Incidental findings* – Term applied in the case of genetic or genomic analyses to mutations or variations that can have clinical implications, but which are discovered unintentionally during tests being performed for an unrelated medical condition. Not all these findings can be interpreted at the time and can have an uncertain meaning.

Integrome – Totality of all the integrated 'omes' (genome, transcriptome, proteome, metabolome, etc.).

P4 medicine – Definition proposed by Hood and Friend as an acronym of Preventive, Predictive, Personalized, Participatory.

Systems medicine - An interdisciplinary field of medicine that analyses the systems of the human body as part of an integrated whole, incorporating genetic, biochemical, physiological, and environmental interactions.

Precision medicine – A medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient. It is often used as a synonym for personalised medicine.

Metabolome – Totality of the **metabolites** of a biological organism, that is, of all the substances that can take part in the processes of an organism.

Monofactorial (**monogenic**) – Trait regulated by only one gene.

NGS*, Next Generation Sequencing* – Second generation sequencing, new genomic analysis techniques.

Genetic polymorphism – Common genetic variation, occurring in at least 1% of the population.

Proteome – Entire set of **proteins** of an organism or a biological system, or the proteins produced by the **genome**

Screening – Identification of persons with a disease or who are carriers of the gene of a disorder in a population.

Segregation (analysis of) – Study of the modalities whereby a disease or trait is transmitted in a family, in order to establish an inheritance model.

SIGU, Società Italiana di Genetica Umana – Italian Society of Human Genetics

Predictive test – It measures the susceptibility or resistance of a person to a disease (usually with late onset), that is different from the average general population.

Pre-symptomatic test - It finds out whether a person has inherited a genetic disorder before it becomes clinically evident (this includes also 'late onset' genetic disorders

Transcriptome – Total set of transcripts (RNA messengers or mRNA) in a given organism, or cell type.

VUS, *Variant of Uncertain Significance* – A type of *incidental findings*, to which at that moment a certain significance (normal or pathological) can be given.

WES*, Whole Exome Sequencing* – Sequencing of the exome, corresponding to about 1% of the genome where the codifying genomes are to be found.

WGS, *Whole Genome Sequencing* – Sequencing of the entire genome.