Informed Consent in Genomic Research: The Iterative Feedback Model

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Informed Consent in Genomic Research: The Iterative Feedback Model

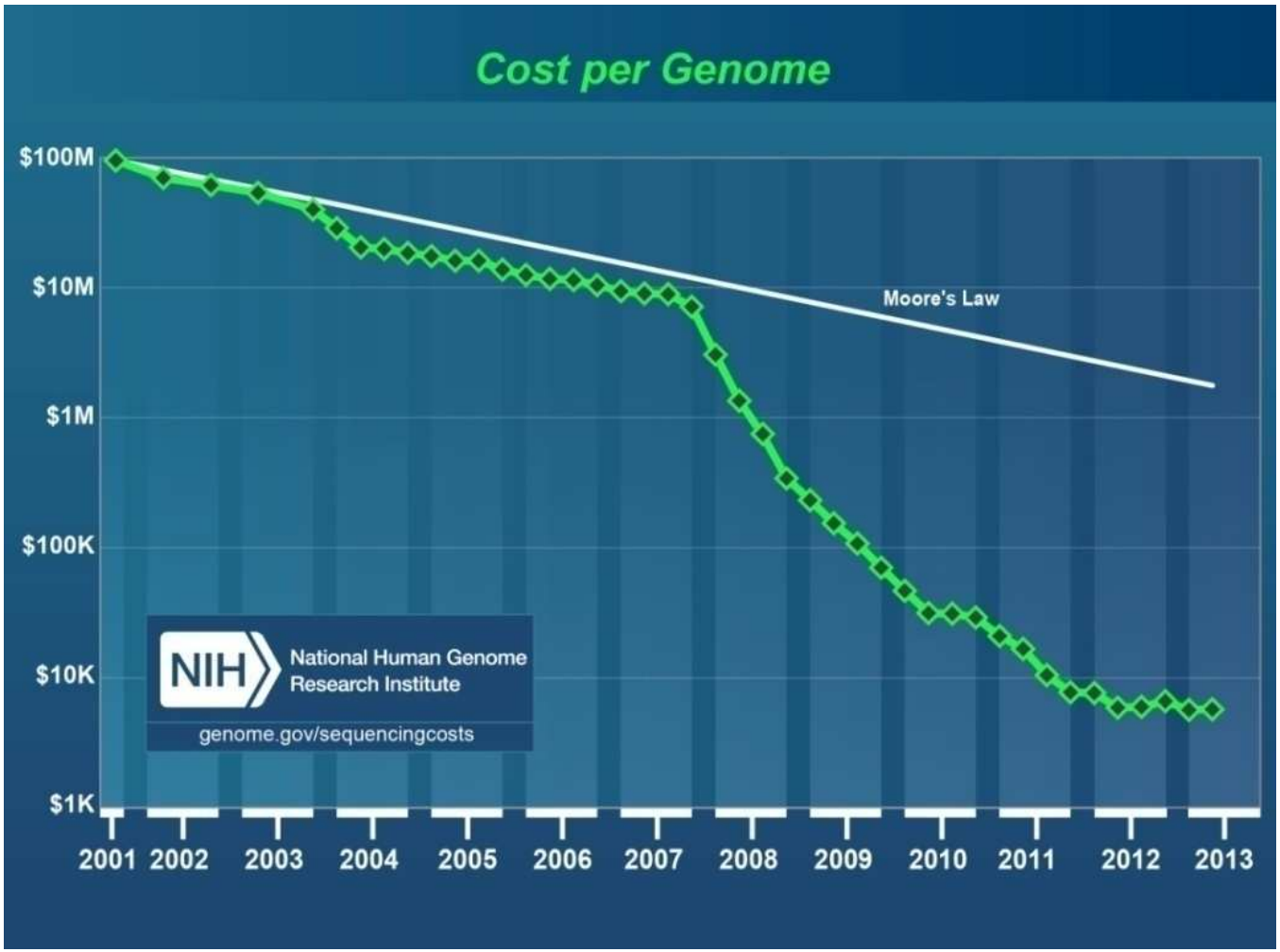
August 14, 2015

Felicitas Holzer, M.Sc.

Content

- **Introduction**
- Justification of the iterative feedback model
- Development of the iterative feedback model

Sequencing Technologies and the 1000 $ Genome

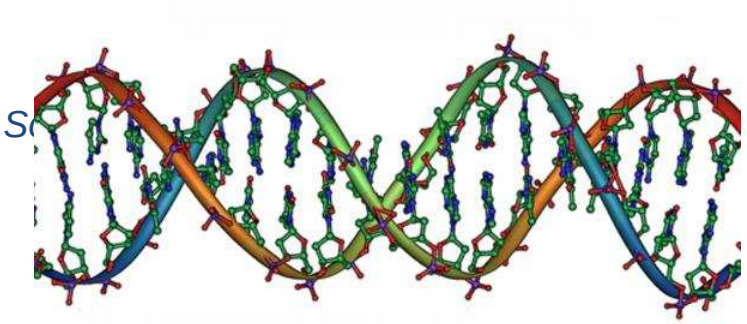


Source: National Human Genome Research Institute (2015)

Genome Wide Assocation Studies (GWAS)

Genome Wide Association Studies

- Subtype of human health research using WGS/WES procedures
- Association of large number of genetic variants with phenotypic traits



Genomics england

Source: University of Cambridge, Research. http://www.cam.ac.uk/research/news/

Sequencing the human genome/exome

Some challenges of genome-wide data collection in research

- Obligations towards third parties
- Confidentiality and data protection
- Storing, sharing and distributing genomic information
- Disclosure of incidental findings

Incidental findings

Definition

"[...] a finding concerning ***health or reproductive importance*** and is discovered in the course of conducting research but is ***beyond the aims of the study***. This means that IFs [Incidental Findings] may be on variables not directly under study and may not be anticipated in the research protocol." (Wolf et al. 2008, Eckstein et al. 2014)

Aim

Specific aim

To present a new ***informed consent model*** for the ***disclosure of incidental findings*** to potential individual research participants in human health research study using whole genomic sequencing (**WGS**)/whole exome sequencing (**WES**) **(genomic)** procedures

Hypothesis

The **iterative feedback model** complies with **ethical principles** better than alternative models given the specific characteristics of **genomic data**

- Holzer, F., Mastroleo, I. (2014): “Does the pragmatic model undermine the importance of the ethical obligations involved in information process? A defence of continuous genetic counselling for research participants.” Journal of Medical Ethics (eLetter)
- Holzer, F., Mastroleo, I. (2015): “Support for Full Disclosure Up Front”, The Hastings Center Report 45, no. 1:3

Content

- Introduction
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General structure of the argument

Strategies for the ethical justification of the iterative feedback model

(1) Specifying the informed consent requirement

(2) Analysing characteristics of genomic data

(3) Evaluating informed consent models based on ethical principles

- Commonly found ethical principles in literature
- Comparison of exemplary consent models extracted from literature review and interviews

1. The informed consent (IC) requirement

According to the *standard ethical informed consent requirement* (Eyal 2011), an informed consent model should grant

(1) full transmission of all relevant information

(2) full comprehension of all relevant information

(3) voluntariness

1. Characteristics of genomic data

Characteristics of genomic data

- Heterogeneity
- Irreversibility
- Connectedness
- Uncertainty

Consequences for the return of results (ROR)

- Predictability
- Reach
- Privacy

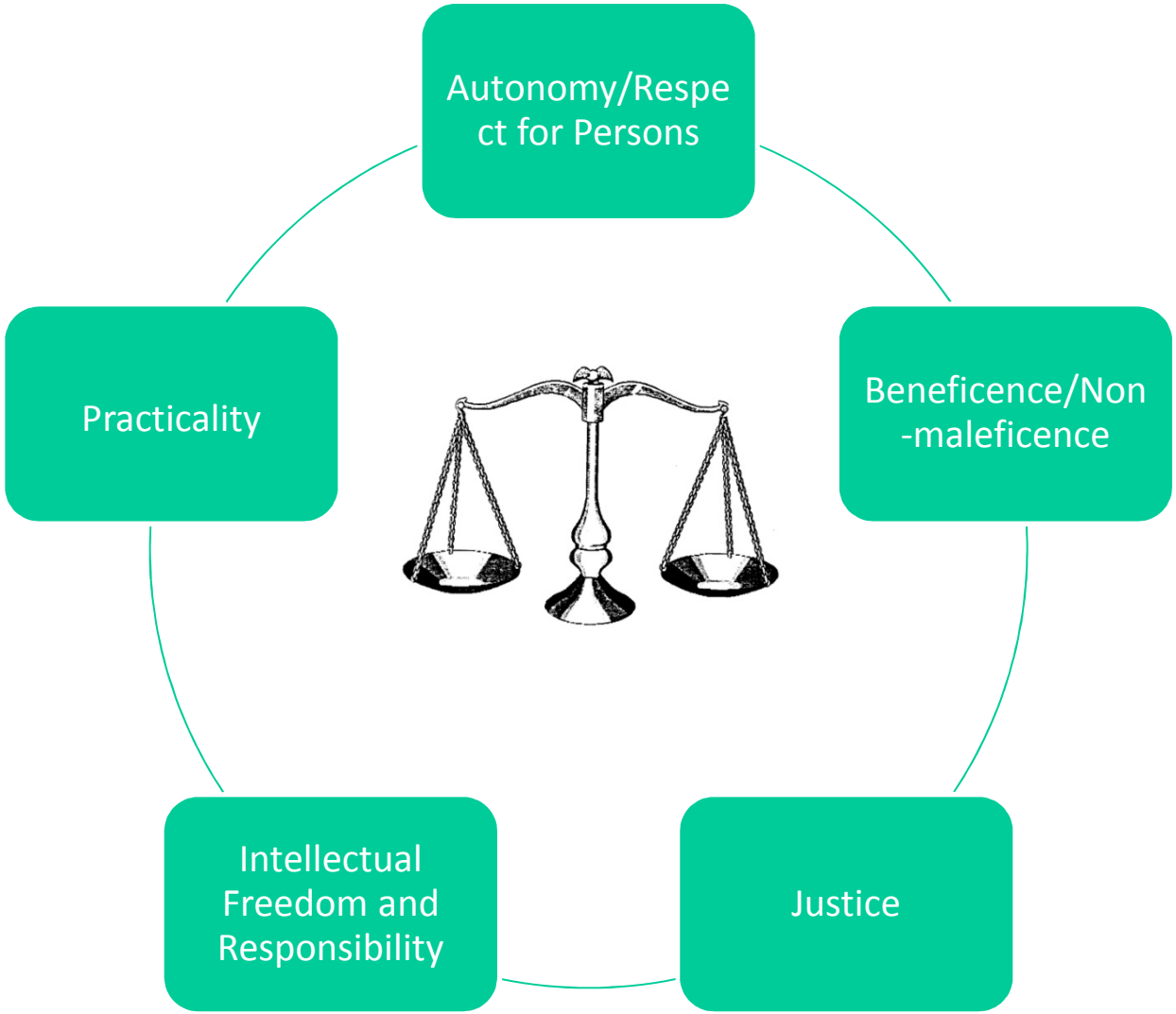
Characteristis and IC requirement

Informed consent requirement	Corresponding characteristics of WGS/WES data, ROR
(1) Full transmission of all relevant information	
- Information important and relevant to participant and relatives	Connectedness, Privacy, Reach
- Delicate and individual information needs a extended consent process	Irreversibility, Heterogeneity, Predictability
(2) Full comprehension of all relevant information	
- Assurance that participants are fully aware of consequences linked to WGS/WES data; impact on psychological health	Predictability, Connectedness, Irreversibility, Uncertainty
- Difficulty to predict if findings contribute to benefits and harms of participant	Heterogeneity
(3) Voluntariness	
- Voluntary consenting on study participation	Personal and delicate information (privacy)

3. Ethical principles (1-3)

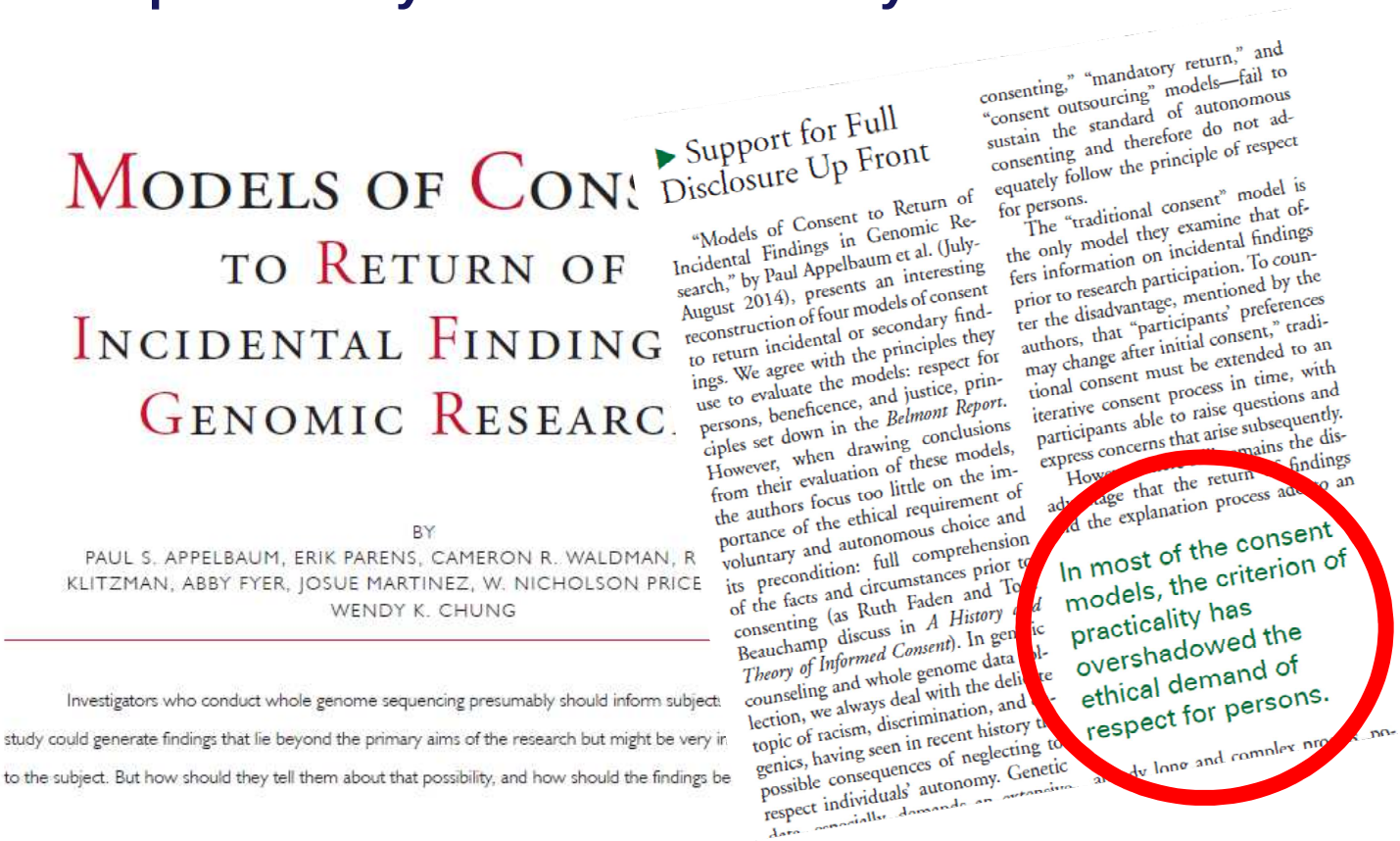
- **Autonomy** (Beauchamp and Childress 2009)/**Respect for Persons** (Belmont Report, National Commission 1979)
- **Beneficence/Non-Maleficence** (Beauchamp and Childress 2009)
- **Justice** (Beauchamp and Childress 2009)
- **Intellectual Freedom and Responsibility** (Presidential Commission 2013)
- **Practicality** (Appelbaum et al. 2014)

3. Ethical principles (2-3)



Autonomy versus Practicality

Can practicality override autonomy?



MODELS OF CONS
TO RETURN OF
INCIDENTAL FINDING
GENOMIC RESEARC

BY
PAUL S. APPELBAUM, ERIK PARENS, CAMERON R. WALDMAN, R
KLITZMAN, ABBY FYER, JOSUE MARTINEZ, W. NICHOLSON PRICE
WENDY K. CHUNG

Investigators who conduct whole genome sequencing presumably should inform subjects
study could generate findings that lie beyond the primary aims of the research but might be very in
to the subject. But how should they tell them about that possibility, and how should the findings be

▶ Support for Full Disclosure Up Front

"Models of Consent to Return of Incidental Findings in Genomic Research," by Paul Appelbaum et al. (July-August 2014), presents an interesting reconstruction of four models of consent to return incidental or secondary findings. We agree with the principles they use to evaluate the models: respect for persons, beneficence, and justice, principles set down in the *Belmont Report*. However, when drawing conclusions from their evaluation of these models, the authors focus too little on the importance of the ethical requirement of voluntary and autonomous choice and its precondition: full comprehension of the facts and circumstances prior to consenting (as Ruth Faden and Tom Beauchamp discuss in *A History and Theory of Informed Consent*). In genetic counseling and whole genome data collection, we always deal with the delicate topic of racism, discrimination, and eugenics, having seen in recent history the possible consequences of neglecting to respect individuals' autonomy. Genetic

consenting," "mandatory return," and "consent outsourcing" models—fail to sustain the standard of autonomous consenting and therefore do not adequately follow the principle of respect for persons.

The "traditional consent" model is the only model they examine that offers information on incidental findings prior to research participation. To counter the disadvantage, mentioned by the authors, that "participants' preferences may change after initial consent," traditional consent must be extended to an iterative consent process in time, with participants able to raise questions and express concerns that arise subsequently.

In most of the consent models, the criterion of practicality has overshadowed the ethical demand of respect for persons.

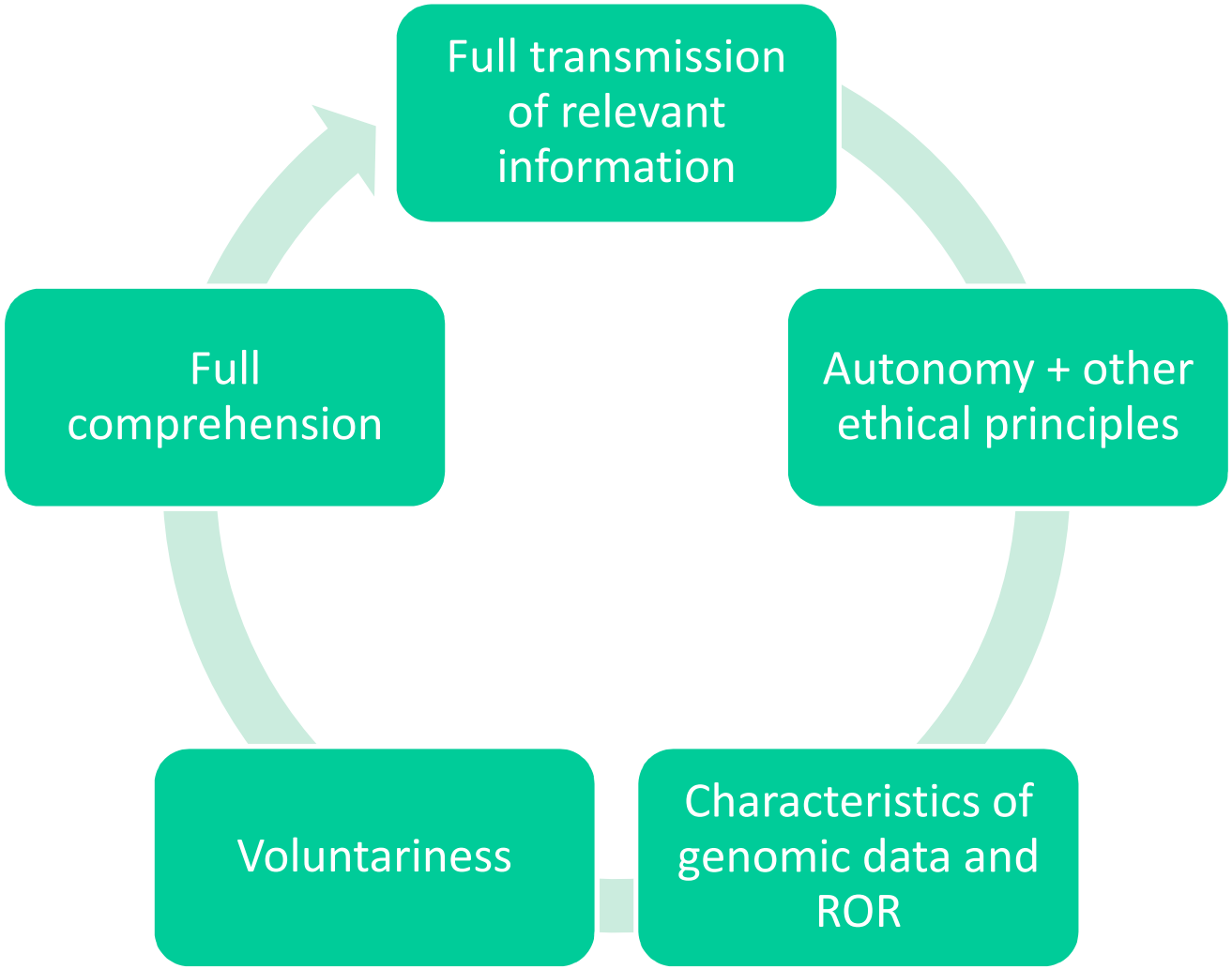
3. Ethical principles (3-3)

Conclusion: Ethical evaluation of informed consent models

Taking into account the **evaluation of prototypic informed consent** models (Appelbaum 2014), I argue for

- Extensive information transmission prior to research participation (***autonomy***)
- Researchers are responsible to return results (ROR) (***justice, intellectual freedom and responsibility***)
- Extensive counselling aiming for minimization foreseeable harm, maximize possible benefit (***Beneficence/Non-maleficence***)

General argument



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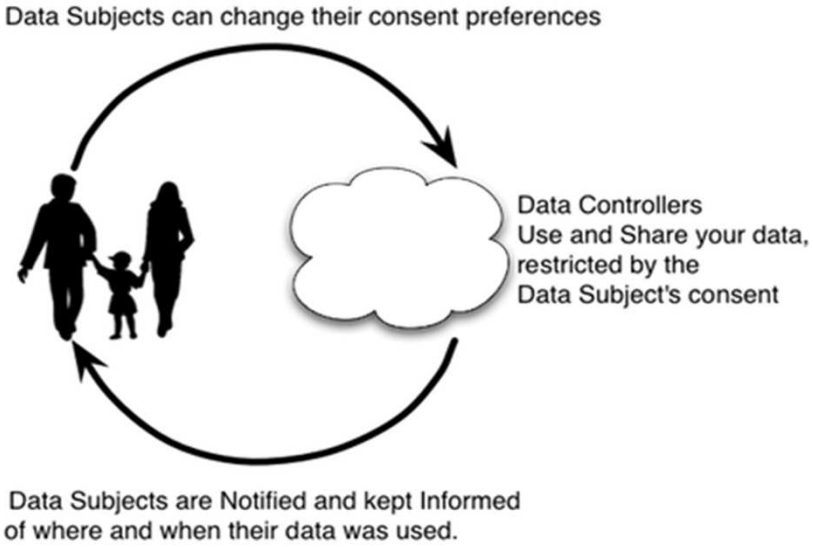
Relying on a continuous counselling process

The dynamic consent model



EJHG Open

European Journal of Human Genetics (2015) 23, 141–146

www.nature.com/ejhg

ARTICLE

Dynamic consent: a patient interface for twenty-first century research networks

Jane Kaye*,[1], Edgar A Whitley[2], David Lund[3], Michael Morrison[1], Harriet Teare[1] and Karen Melham[1]

Biomedical research is being transformed through the application of information technologies that allow ever greater amounts of data to be shared on an unprecedented scale. However, the methods for involving participants have not kept pace with changes in research capability. In an era when information is shared digitally at the global level, mechanisms of informed consent remain static, paper-based and organised around national boundaries and legal frameworks. Dynamic consent (DC) is both a specific project and a wider concept that offers a new approach to consent; one designed to meet the needs of the twenty-first century research landscape. At the heart of DC is a personalised, digital communication interface that connects researchers and participants, placing participants at the heart of decision making. The interface facilitates two-way communication to stimulate a more engaged, informed and scientifically literate participant population where individuals can tailor and manage their own consent preferences. The technical architecture of DC includes components that can securely encrypt sensitive data and allow participant consent preferences to travel with their data and samples when they are shared with third parties. In addition to improving transparency and public trust, this system benefits researchers by streamlining recruitment and enabling more efficient participant recontact. DC has mainly been developed in biobanking contexts, but it also has potential application in other domains for a variety of purposes.

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(Centre for Health, Law and Emerging Technologies (HeLEX), University of Oxford, London School of Economics and Political Science, HW Communications Ltd)

The iterative model

- based on dynamic consent model
- complemented by a guided and countinuous counselling process

Which findings should be disclosed?

The “3V” framework (Eckstein et al. 2014)

Figure 1

The “3V” Framework for Analyzing the Ethics of Disclosing Secondary Findings

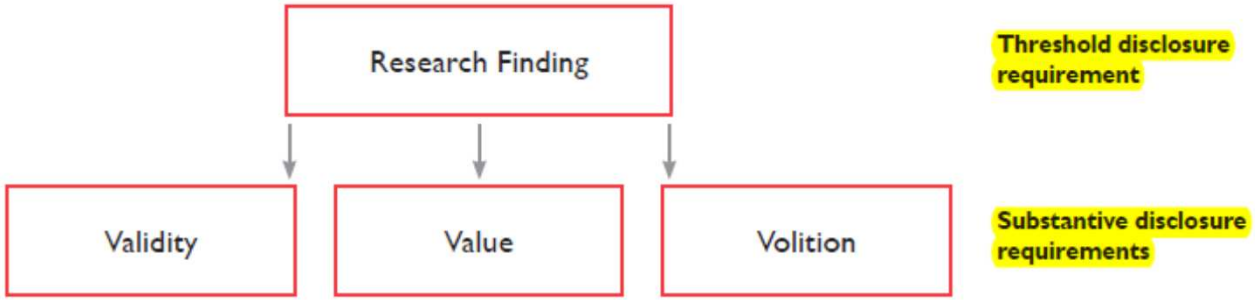
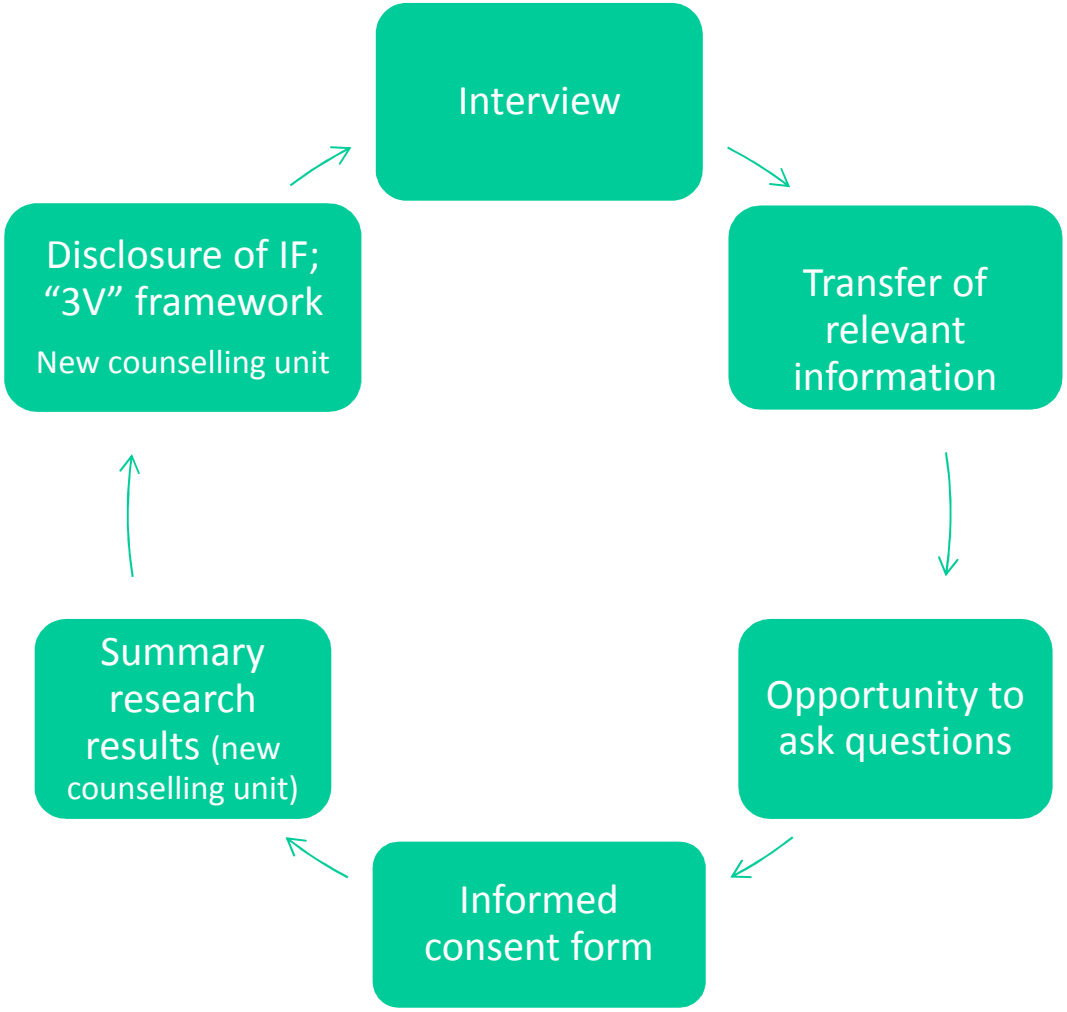


Figure 1: The “3V” Framework for Analyzing the Ethics of Disclosing Secondary Findings. As a threshold requirement to fall within the scope of a disclosure framework, information must constitute a “research finding.” To meet the substantive requirements to qualify for disclosure, research findings must meet the requisite requirements of validity, value, and volition.

Validity	**Scientifically valid findings**
Value	**“[...] a normative property regarding the worth, significance, or utility of a research finding (whether subjective or objective)”**
Volition	**Participants’ preferences**

The iterative feedback model (1-2)

Crucial steps in the informed consent process – the iterative feedback model



The iterative feedback model (2-2)

Disclosure of Incidental Findings fulfilling the "3V"

Data Base 2	Data Base 1	Data Base 3
• **Known Associations** (Literature, Data Bases, Data Banks)	• **Individual Genome** (Genome Data Base of research study)	• **New Discoveries** (Literature, Data banks)

Step 1: check once in Data Base 1 and 2 for relevant findings in individual Genomes

*Step 2: check **repetitively** in Data Base 1 and 3 for relevant variants in individual Genomes*

Inform participant

Why the “iterative” model? (1-2)

Why does an “iterative” model comply with the ethical informed consent requirement for research projects using WGS/WES procedures?

Characteristics of WGS/WES data

- Predictability/Uncertainty
    - genotype-phenotype associations that are not yet known but at a future point in time
- Heterogeneity
    - information can be easily overlooked; iterative communication process aims for information transmission that is as complete as possible
- Connectedness
    - e.g. preferences concerning reproductive decisions can arise later in the course of the research conduct

Why the “iterative” model? (2-2)

Why does an “iterative” model comply with the ethical informed consent requirement for research projects using WGS/WES procedures?

Autonomy

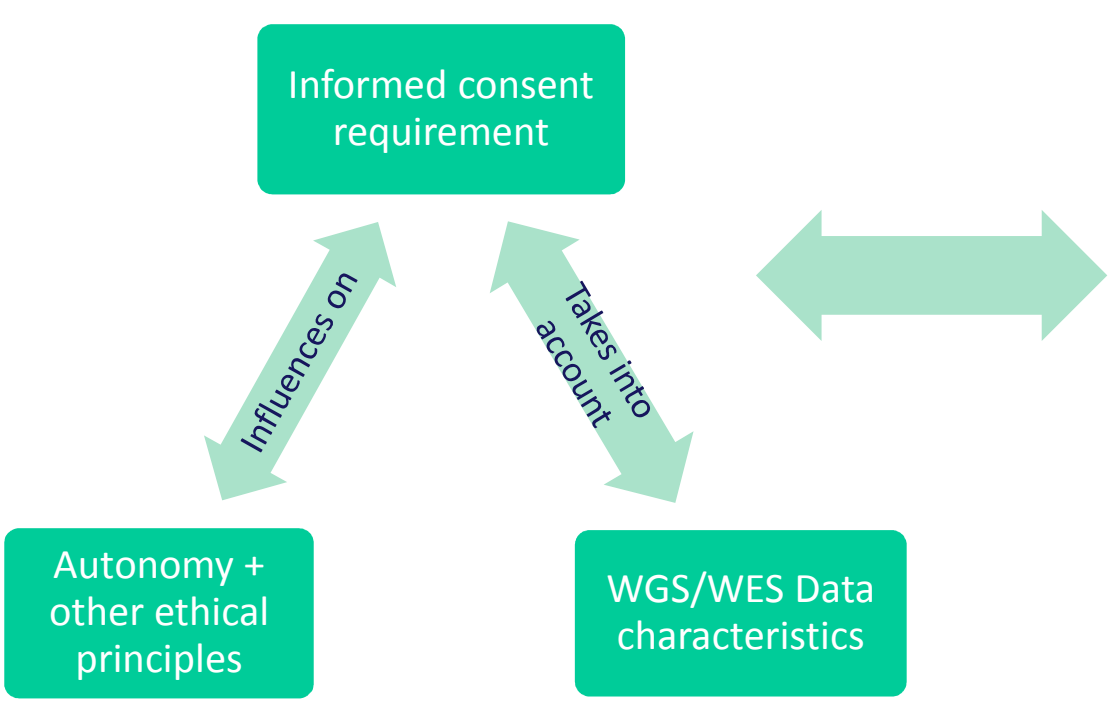
- Participants’ preferences can change over time

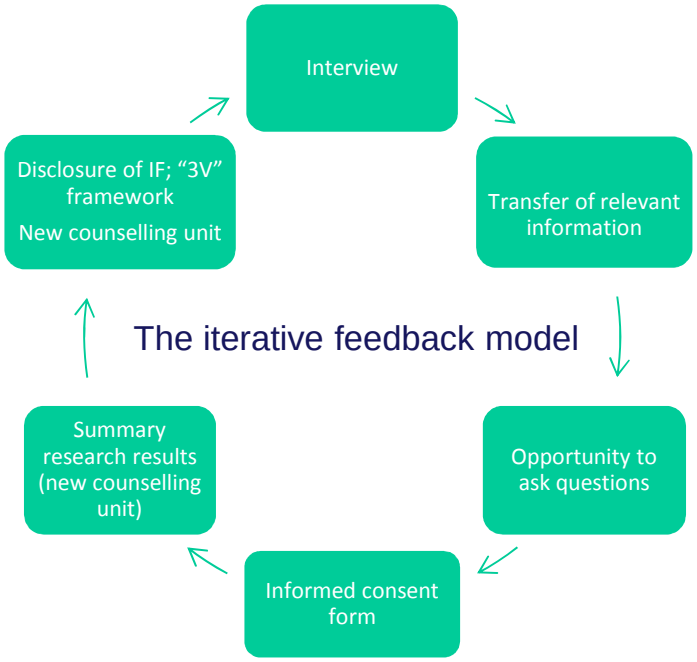
Information disclosure and comprehension

- Information transmission and comprehension improve if embedded in an iterative process

Summary

"The new iterative feedback model complies with ethical principles better than alternative models given the specific characteristics of WGS/WES data" (Hypothesis)





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Thank you
Muchas gracias
Danke
धन्यवाद

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SUPPLEMENT

1. Characteristics of genomic data (3-3)

Informed consent requirement	Corresponding characteristic s of WGS/WES data, ROR
(1) Full transmission of all relevant information	
- Information important and relevant to participant and relatives	Connectedness, Privacy, Reach
- Delicate and individual information need a extended consent process	Irreversibility, Heterogeneity, Predictability
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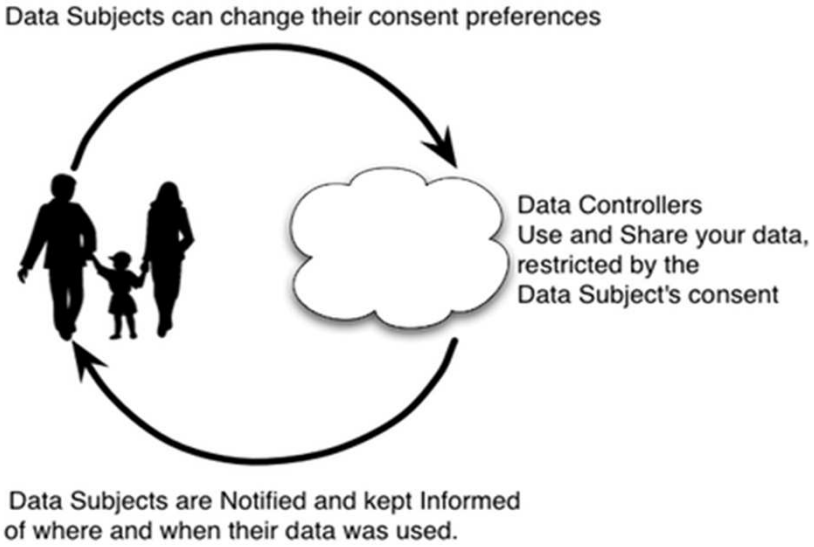
- Assurance that participants are fully aware of consequences linked to WGS/WES data; impact on psychological health	Predictability, Connectedness, Irreversibility, Uncertainty
- Difficulty to predict if findings contribute to benefits and harms of participant	Heterogeneity
(3) Voluntariness	
- Voluntary consenting on study participation	Personal and delicate information (privacy)

Development of the iterative feedback model (1-3)

The dynamic consent model



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The iterative model

- based on dynamic consent model
- complemented by a guided and countinuous counselling process

The iterative feedback model (3-3)

Communication Process between researcher and counsellor

Data Base 2	Data Base 1	Data Base 3
• **Known Associations** (Literature, Data Bases, Data Banks)	• **Individual Genome** (Genome Data Base of research study)	• **New Discoveries** (Literature, Data banks)

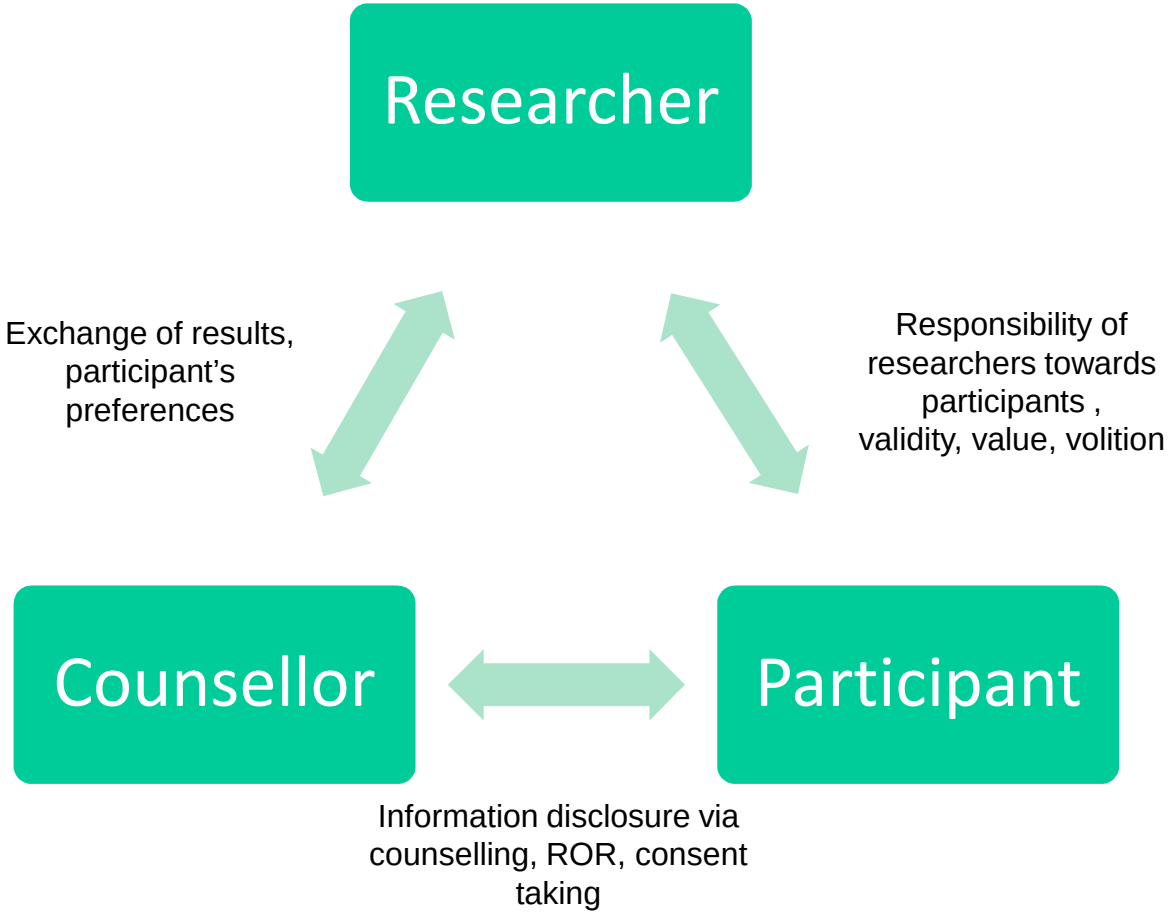
Step 1: check once in Data Base 1 and 2 for relevant findings in ind. Genomes

Step 2: check repetitively in Data Base 1 and 3 for relevant variants in individual Genomes

Inform participant

The iterative feedback model (2-2)

“3 agents approach”



(1) Practicality (1-2)

Resource consumption even years after the study conduct (counselling obligations prior to, during and after trial)

Is the iterative feedback model cost-effective?

Cost-effectiveness (Cost-benefit-analysis)

- Measures health interventions in a representative monetary value
- Compares outcomes (e.g. life years gained, deaths avoided) with costs

(1) Practicality (2-2)

- Can we estimate costs/benefits prior to research conduct?
- Should former health care costs be taken into consideration?
- Funding obligations by other agents than researchers
- Supportive tools (e.g. Software tools for screening of data bases, data banks; automated communication processes)

Which findings should be disclosed? (1-2)

- **Primary** findings researchers deliberately seek for
- **Anticipatable** findings associated with the test procedure
- **Anticipatable** findings recommended to seek for by expert commission
- **Unanticipatable** findings, not known to be associated with the test procedure

TYPE OF RESULT DISCOVERED	DESCRIPTION	EXAMPLE
Primary Finding	Practitioner aims to discover A, and result is relevant to A	In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered
Incidental Finding: *Anticipatable*	Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place	Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related[53]
Incidental Finding: *Unanticipatable*	Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place	When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not know-able at the time a previous sample was submitted[54]
Secondary Finding	Practitioner aims to discover A, and also actively seeks D per expert recommendation	ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits[55]
Discovery Finding	Practitioner aims to discover A through Z by employing a test or procedure designed to detect a broad array of results	A "wellness scan," a whole body computed tomography (CT) scan, is intended to discover any abnormal finding throughout the body[56]

Source: Presidential Commission 2013: 27

(3) Ancillary care obligations (1-2)

Ancillary care (Richardson and Belsky 2004) is defined as

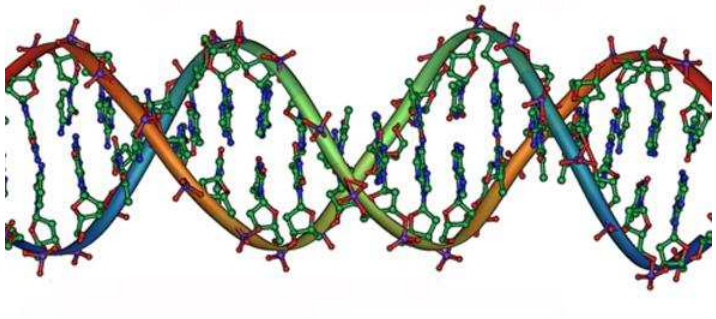
- "Care not required by sound science, safe trial conduct, morally optional promises, or redressing subject injury"
- Therapeutic consequences, if there are treatment options or preventive measures, resulting from the disclosure of findings

(3) Ancillary care obligations (2-2)

Future work should address (cf. Merritt 2011)

- If there are ancillary care obligations (referring to general principles)
- If yes, for which type of findings are they mandatory
- Lower and upper limits of the extension of the obligations (should be non-arbitrarily located)

Case Study: The Rare Diseases Genomes Project



Source: University of Cambridge, Research. http://www.cam.ac.uk/research/news/

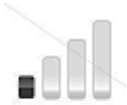
The rare diseases genomes project, U.K.

- 3 years project, started in 2013
- Pilot project for Genomics England (Aim: to sequence 100,000 genomes in total)
- Sequencation of 10,000 genomes of individuals with rare genetic diseases
- Supported by University of Cambridge, Genomics England and Illumina

- **GWAS (Genome Wide Association Study)**
  - Subtype of human health research using WGS/WES procedures
  - Association of large number of genetic variants with phenotypic traits

2. Ethical principles (2-3)

My ethical analysis of to prototypic models (Appelbaum et al. 2014)

	Autonomy	Beneficence /Non-maleficene	Justice	Intellectual freedom/responsbility	Practicality
Traditional consent model					
Staged consent model					
Mandatory return model					
Outsourcing model	**Depending on counselling service**	**Depending on counselling service**			**Depending on counselling service**

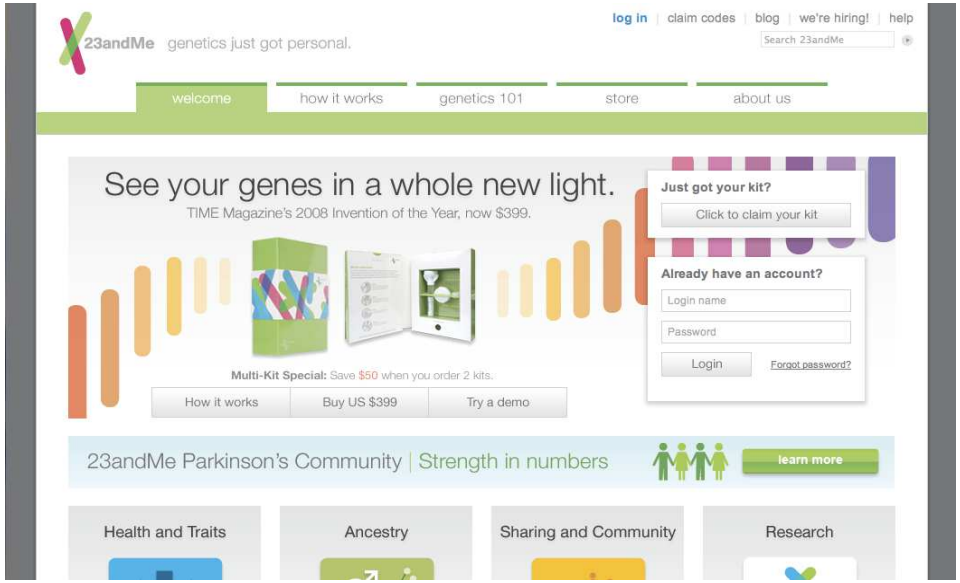
Direct-to-Consumer Tests

Companies offering genetic screening for several features

- intelligence, aptitudes, **monogenetically caused diseases** etc.
- Risk factors and optimization of drug therapies
- Incidental findings only partially reported (ACMG)

easyDNA

23andMe



Source: www.23andme.com (2013)

Polymerase Chain Reaction

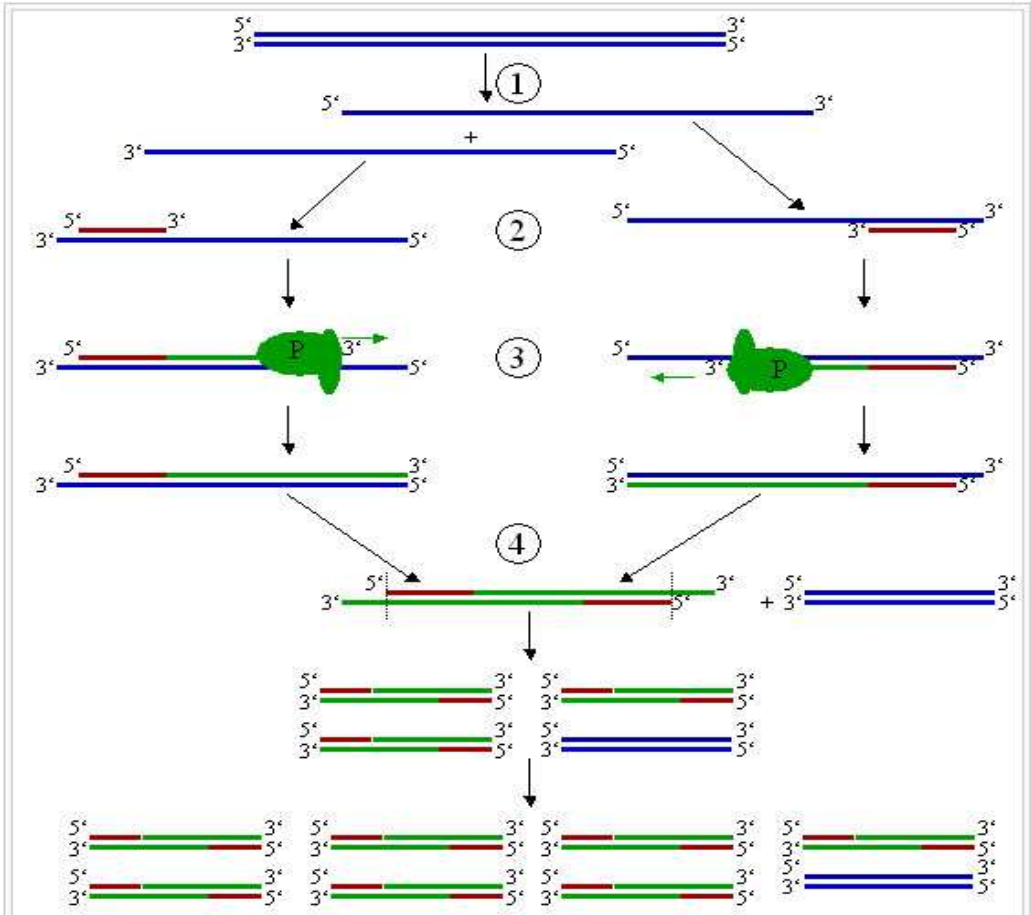


Figure 2: Schematic drawing of the PCR cycle. (1) Denaturing at 94-96°C. (2) Annealing at (eg) 68°C. (3) Elongation at 72°C (P=Polymerase). (4) The first cycle is complete. The two resulting DNA strands make up the template DNA for the next cycle, thus doubling the amount of DNA duplicated for each new cycle.

Source: serc.carleton.edu (2013)