



Responsible Implementation of Genomic Testing for Rare Kidney Disorders

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**KDIGO Controversies Conference on Common Elements in
Uncommon Kidney Diseases – 17 June 2016**

Disclosure of Interests

Employment by

- VU University Medical Centre, Amsterdam, NL

where DNA-testing is performed for high risk of serious disorders
for part of the Netherlands

No financial relationships with commercial companies (within last 3 years) related to
the topic of this presentation



Overview

- Responsible implementation
 - Realize (some of) the promises to the tax payers
 - Do what we know in a responsible way
- Sequencing technologies
 - Many genes for a relatively low price
 - Unsolicited findings and Variants of Uncertain Significance
- Rare diseases
 - Data sharing and registries

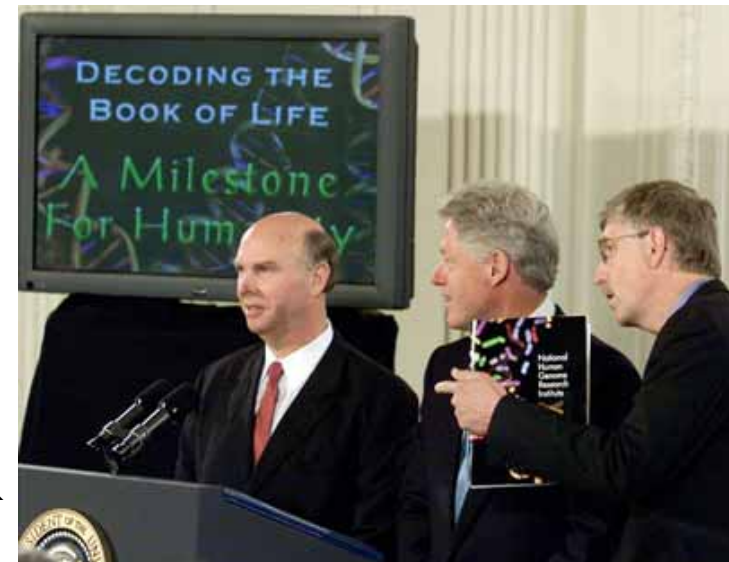


2000: genome sequence published

Bill Clinton: We are here to celebrate the completion of the first survey of the entire human genome ...

With this profound new knowledge, humankind is on the verge of gaining immense, new power to heal. Genome science will have a real impact on all our lives -- and even more, on the lives of our children.

It will revolutionize
the diagnosis, prevention
and treatment of most,
if not all, human diseases.



Collins FS (Right at photo). Nature 2010 &
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*KDIGO Controversies Conference on Common Elements in Uncommon Kidney Diseases
June 16 - 19, 2016 | Amsterdam, Netherlands*



Collins, 10 years later

(Nature 2010;464:674-5)

Has the revolution arrived?

The consequences for clinical medicine, however, have thus far been modest.

Those who somehow expected dramatic results overnight may be disappointed, but should remember that genomics obeys the First Law of Technology:

we invariably overestimate the short-term impacts of new technologies and underestimate their longer-term effects.

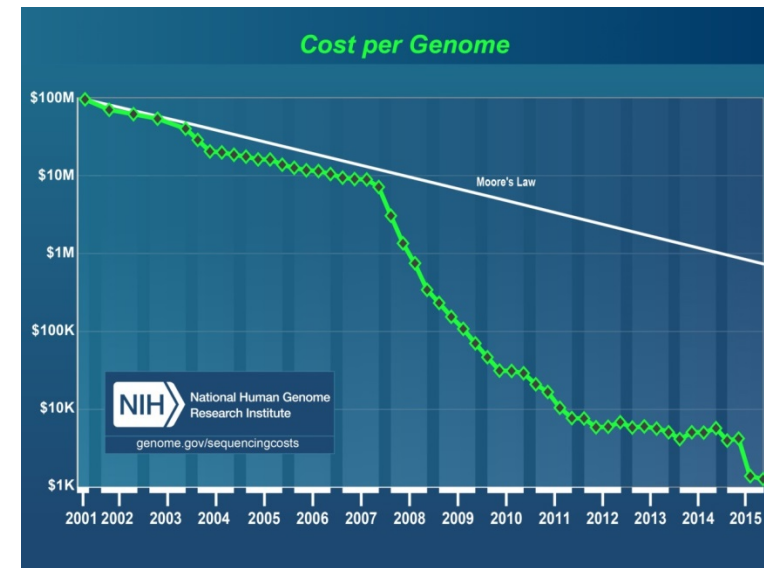
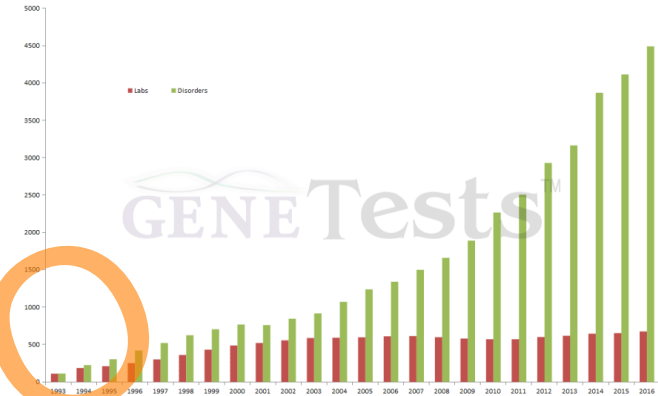
Responsible implementation

- **Efficient**
 - Waste of time, effort and finances are minimized
- **Effective**
 - Produces intended results
- **Robust and sustainable**
 - Anticipates changes in the future
- **Translating genome-based information into health care practice (Do what we know)**



Sequencing technologies

- More DNA tests available
- Price of DNA testing decreases
- Number of persons for whom DNA testing could potentially be relevant increases
- Fixed budgets
- Prioritization needed
- Mainstreaming needed



More tests for a lower price – better?

- Greater potential to identify the genetic component of health problem
- Unsolicited findings
 - BRCA in child with developmental delay
 - Kidney problem in child with multiple congenital anomalies
- VUS: Variants of uncertain significance



European Journal of Human Genetics (2013) 21, 580–584
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www.nature.com/ejhg

POLICY

Whole-genome sequencing in health care

Recommendations of the European Society of Human Genetics

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on behalf of the ESHG Public and Professional Policy Committee



Unsolicited findings

- Not an **incident**: the technology causes many UFs
- Not always **secondary**: sometimes no answer to the clinical question and yet some findings you were not looking for
- In the clinical context - challenges of handling vast amounts of information, most of which may not be directly relevant for the patient...
- Use filters to select relevant variants after sequencing .. not too soon or too restrictive .. hinder the diagnostic process

Unsolicited findings

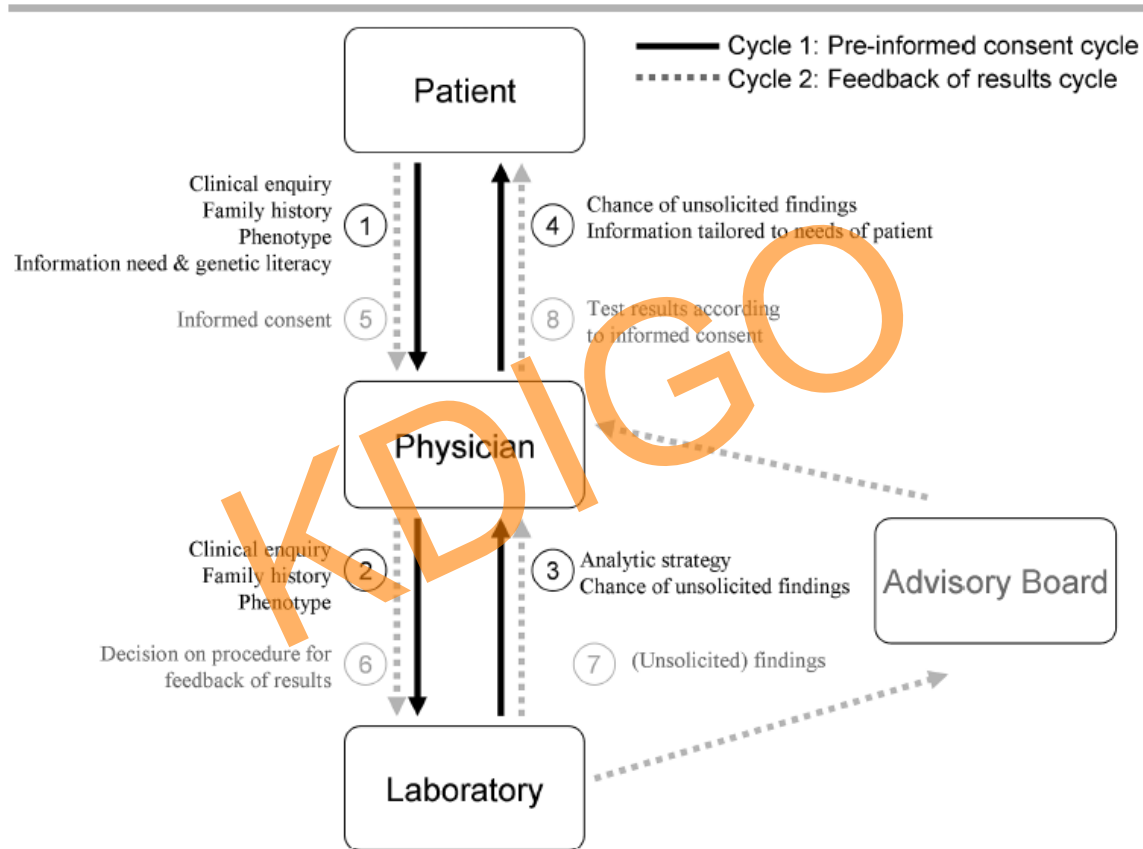


Figure 1. Cooperation and communication between different parties involved in the informed consent procedure for NGS in diagnostics.

Rigter 2013 Hum Mutation

More analyses for a lower price – better?

- (1) ... should set up structures for sharing experiences and establish testing guidelines at local, national and international levels.
(collective learning process)
- (2) When in the clinical setting either targeted sequencing or analysis of genome data is possible, it is preferable to use a **targeted approach** first in order to avoid unsolicited findings or findings that cannot be interpreted. **Filtering** should limit the analysis to specific (sets of) genes. Known genetic variants with limited or no clinical utility should be filtered out (if possible neither analyzed nor reported).
- (3) The use of genome-wide arrays or **WGA** requires a **justification** in terms of necessity (the need to solve a clinical problem) and proportionality (the balance of benefits and drawbacks for the patient).

Van El EJHG 2013

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 - Unsolicited findings and Variants of Uncertain Significance
- **Rare diseases**
 - Data sharing and registries



Rare diseases

- After GWAS era (looking for associations of common diseases - common variants) NGS fits better!
- General principles
 - one test for anything (although expertise for analysis required)
 - increase of open access mentality - sharing data globally
<https://genomicsandhealth.org/>
 - Mechanisms in place to find one more patient with same mutation – Global Alliance for Genomics and Health (GA4GH) – Matchmaker Exchange e.g.

Rare diseases

- Implementation requires **registration** – how can all children with condition XXX profit from new test or treatment?
- **Recontact?** Can we go back to patients?
- **Classification?** Morphology or relation to gene(response)?
- **Public or private?** Apart from open access models (GA4GH) also companies with registries, not all of which are shared

Conclusion

- Many opportunities
- More is not always better: filter (limited resources)
- Organize settings for collective learning
- Register to know target group
- Think global

