

# Responsible Implementation of Genomic Testing for Rare Kidney Disorders

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### **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

DECODING THE

BOOK OF LIFE

children.

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

Collins FS (Right at photo). Nature 2010 & © AP PHOTO/RON EDMONDS



# 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.



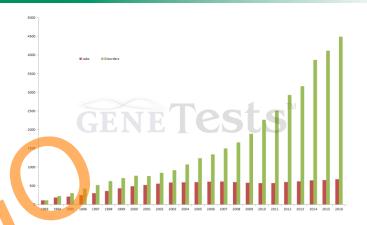
### Responsible implementation

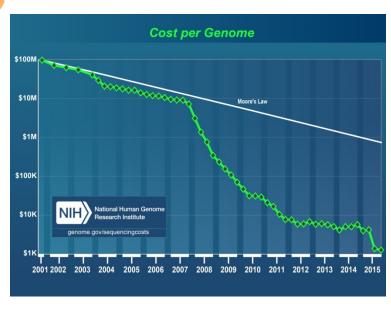
- Efficient
  - Waste of time, effort and finances are minimized
- Effective
  - Produces intended results
- Robust and sustainable
  - Anticipates changes in the future
- Translating genome-based information into health care practice (Do what we know)



### 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



Cartoon festival Knokke 2014 With permission of Borry & Matthijs



### 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



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www.nature.com/ejh

#### POLICY

#### Whole-genome sequencing in health care

Recommendations of the European Society of Human Genetics



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### **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**

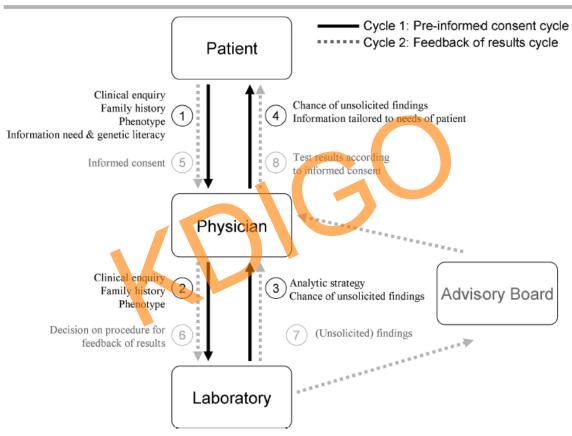


Figure 1. Cooperation and communication between different parties involved in the informed consent procedure for NGS in diagnostics.

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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#### 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 <a href="https://genomicsandhealth.org/">https://genomicsandhealth.org/</a>
  - Mechanisms in place to find one more patient with same mutation Global Alliance for Genomics and Health (GA4GH) – Matchmaker Exchange e.g.



alth.org/work-products-demonstration-projects/matchmaker-exchange- 🔎 🔻 🗎 🗸 🛮 🚺 Matchmaker Exchange | Gl... 🗶

Catalogue of Activities -Mendelian

Consent Codes

Consent Policy

Consent Tools

Data Sharing Lexicon

Family History Collection Tools - Statement of Best Practice

Family History Tool Inventory

File Formats: CRAM

File Formats: SAM/BAM

File Formats: VCF/BCF

Framework for Responsible Sharing of Genomic and Health-Related Data

Genomics API

Matchmaker Exchange API

Metadata: Specification

#### About this Project

Matchmaker Exchange is a collaborative effort to address the common challenge of exome and genome sequencing in both the research and clinical settings wherein the majority of cases lack a clear etiology after initial analysis. For such cases, finding just a single additional case with a deleterious variant in the same gene and overlapping phenotype may provide sufficient evidence to identify the causative gene. Currently, multiple research and clinical laboratories and rare disease consortia independently collect data, but the result is fragmentation of efforts making the aggregation of similar cases difficult.

To address this challenge a meeting was organized by the International Rare Diseases Research Consortium (IRDIRC) and the Clinical Genome Resource (ClinGen) program, resulting in the launch of an open collaboration called the 'Matchmaker Exchange' in October 2013. This



Last Updated: September 14th, 2015

involves a large and growing number of teams and projects (see accompanying figure) working towards a federated platform (Exchange) to facilitate the matching of cases with similar phenotypic and genotypic profiles (matchmaking) through standardized application programming interfaces (APIs) and procedural conventions.

The Matchmaker Exchange project is being supported by the database participants involved as well as IRDIRC, ClinGen, and GA4GH.

#### Resources

#### 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

