What distinguishes research from clinical services.

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Categories of research

- Clinical research
- ”Close to clinical situations”
- Biobank research

My own background

- Clinical background in syndromology and rare disorders and familial consequences.
- Worked extensively with Huntington´s disease from most viewpoints - which has learnt me: Every decision in genetic disorders has consequenses for others, not only ”patient” but third parties also.
- Have worked closely with organisations for families with rare disorders

Criteria and Requirements

- What ethical issues should ERB identify:
- Predictive value for diagnosis and treatment
- Risk to relatives and possible reproductive options
- Uncertainty of information
- Incidental findings- (IF)

First situation

- One/handfull of patients- Diagnostic label but no gene- no pathophysiological mechanism known (possible pathway?)
- ”Everything possible done”:(Expert evaulation, microarray CGH etc)
- Sampling of affected child and parents and maybe healthy sibs

Clinical causation

- Autosomal dominant mutation- new gene alteration found in same gene in all/most affected.
- Result : Everyone happy - low recurrence risk
- Autosomal recessive: Both parents carriers and 25% recurrence risk for further children, but prenatal diagnostics likely to be offered.
- ”In the best case”: Family and clincians happy.
- ”No difference from ordinary genetic testing”

NGS is still not a ”standard method” for clinical use

- Results should be independently confirmed by other methods by personell with medical genetic expertice on spesific condition.
- Is genetic variant found the causative agent- expressed on protein level?
- Functional studies often neccessary and time consuming- Variants of uncertain significance”-VUS

Caveats

- Most ”such disorders” likely to be heterogeneous
- Incidental findings (IF) to be discussed beforehand, but parents would feel that they have ”little to loose” and much to gain by NGS

Research in ”close to clinical situations”

- A) Intermediate number of participants(<100?)
- B) Suspicion of certain disorders from health registers. Must have consented to be contacted for further investigations and for verification of medical information
- Establishing clinical validation and utility of research in small samples- i.e.- how well does the testpredict the presence/absence of a disease and should it be treated differently if a spesific genetic change is present or absent

Practical examples

- Pharmacogenetics: Nonresponders/respon.
- Cancer treatment: HLA in melanoma and breast cancer responses to Herceptin in HER-2 positive tumors
- Cardiomyopathi- panel
- Long QT- panel
- Muscular dystrophy

Problem

- Could subjects be contacted because of selective genetic information?
- Larger problem: How different is genetic information for other medical information- apart from the risk to other family members?

Incidental findings

- Factors to consider:
- Magnitude of risk?
- Predictive power
- Seriousness of disorder
- Treatment availability? Now or in near future?
- Family history of disorder?
- Local law?

What about carrier states for recessive disorders

- We are all carriers for 3-5 serious recessive genes- some frequent in the population like Cystic fibrosis and Spinal muscular atrophy (frequency around 1/35) – others rarer.
- Previous experiences of carrier identification partly showing stigmatizing effects

Incidental findings- principles for handling 1

- No feedback given under any circumstances (too easy?)
- Local ethical advisory board looking into spesific findings to decide if reasons for feedback to patients/families is sufficient for ”duty to help”
- Then possibly notify ERB of this, before contact with patients (- time consideration usually not urgent)-

Incidental findings- principles for handling 2

- Medical ethical advisory board for incidental genetic findings could consist of ethicist-medical geneticist not involved in cases, molecular biologist and possibly lay person.
- Department of medical genetics should be handling agent.
- Involving General Practioner-? for contact? (depending on local tradition)

Right to know stored health information about yourself

- Sequence cannot be truly anonymised
- Potential for misuse
- Difficult to consent fully for all possible events.
- But big agents(NIH/Wellcome Trust) will require storage as a premise for funding.
- (In Norway an absolute right to know how information about oneself is stored)

Right to know stored health information about yourself

- ”The information should be presented in a way adapted to the subjects abilities and needs”
- It is uncertain to what extent this extends to NGS
- It is easier to produce the data, than making a meaning out of them

Right to NGS- info.

- Whole genome sequence on a memory stick? (Unanalyzed form)
- Incidental findings- not yet confirmed by other methods
- The right to qualified genetic counselling after confirmation of (all?) incidental findings by other methods.
- In Norwegian law: Not clear how far the researcher/clinicians duty extends

How, when and whether to return genetic results to study subjects and families?

- ”One of the thorniest cultural challenges in clinical research” Francis Collins,NIH
- ”We are living in an akward interval where our ability to capture the information often exceed our ability to know what to do with it.

Types of incidental findings

- Disposition for Alzheimer: Analogous til ApoE4 determination- no feedback given. No treatment possible- uncertainty if becoming affected
- Huntington disease: Certainty of disorder – but no treatment p.t. : No feedback given in Norway- but certainly in Nijmegen)
- Severe consequences for research subject and family. Intermediate alleles poses special problems

Types of incidental findings- cont

- BRCA 1/2 - treatment and profylaxis possible – High, but not absolute predictive value.
- Mismatch genes for colon cancer- ditto.
- ”Duty of care and healing” in most cases - family history?

Storage and sharing of data- adults

- Ask beforehand if data can be stored in diagnostic biobank
- Available for further research in future for projects related to spesific condition only, or available in deidentified/anonymized form for general further use
- Shared with other researchers inside EU/EEC or outside- i.e. USA??

Should all NGS projects seek ERB permission beforehand

- Yes p.t?
- Because too many unresolved issues p.t. with respect to predictive incidental findings, storing and sharing of data, possible publication, genetic counseling issues concerning healthy family members used for control, children unable to consent for themselves etc etc.

What should informed consent forms for NGS discuss

- Still a method where no certain answers can be given without confirmation by other methods
- What type of feedback can be expected with respect to main disorder, other diseases in the family and incidental findings and carrier states for recessive diseases

What should informed consent forms for NGS discuss ?-2

- Data storage and possible sharing- specially with respect to databases abroad.
- Reidenitification issues including possible cryptification procedures
- Further use in research
- ”Right to information” stored about onself

Special protection rules for minors ?

- Most research for rare disorders would be performed in children
- Since they are unable to consent for themselves, special considerations are discussed, not only in Norway, for problems discussed above with respect to storing and sharing data.

Beneficial findings (Nature 2012,483,373

- Some incidental findings may save life etc!
- Radiologists screen MRI for incidental findings and give feed-back.
- Commercial marketing is coming tailored on your genomic profile-
- Why should not research praticipants benefit from their genomic findings?

Microbiology

- Complex interplay between genetic disposition to agent and treatment response and resistance development dependent both man, microbiological agent and drug.

Conclusions

- Many unresolved issues.
- But not very different from introduction of previous diagnostic methods like GWAS-genome wide association screening
- High potentials for benefits and misuse.
- Real problems in reuse and storing of data.

Final problem

- Direct to consumer testing outside legal restrictions in EU/EEC area.

- Individual may send samples to commercial actors and have 1.”answers of uncertain validity” and 2.consent to sharing of data in databases