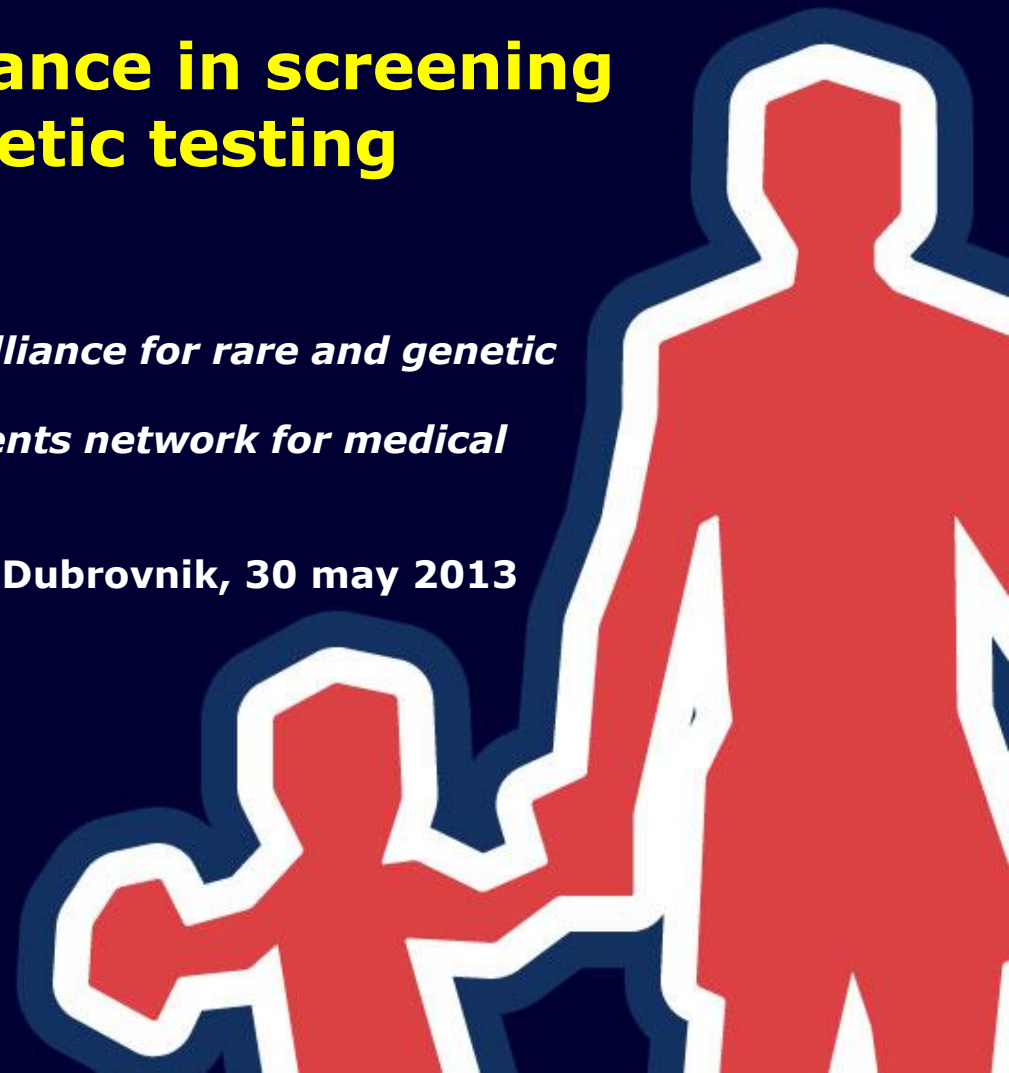
A patient view on ethics and governance in screening and advanced genetic testing

Cor Oosterwijk PhD

Director VSOP: Dutch patient alliance for rare and genetic diseases
Secretary –general EGAN: Patients network for medical research and health

Eurordis membership meeting, Dubrovnik, 30 may 2013



Patients / parents as a partner:

"Nothing about us without us":

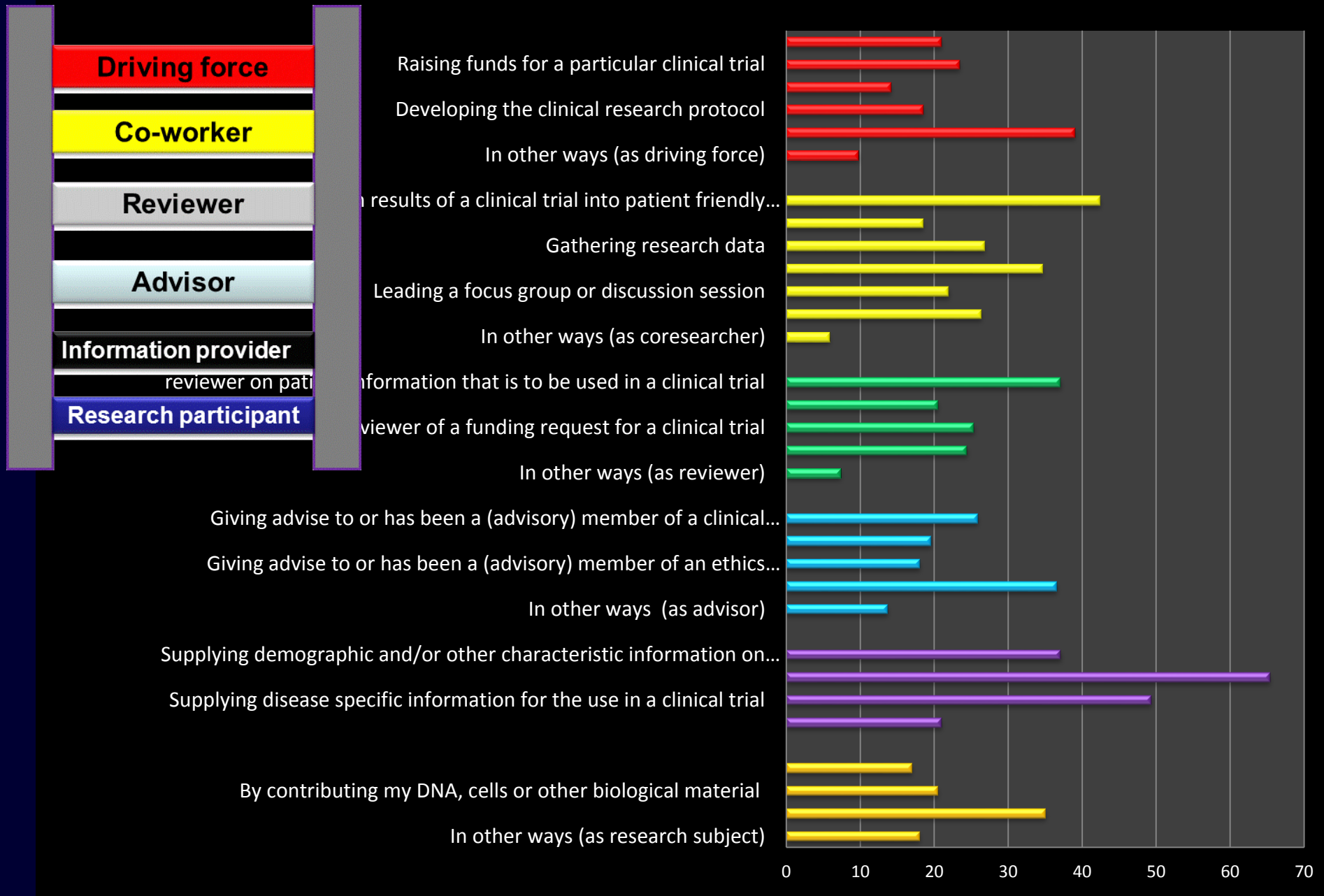
- Health care (policy)
- Genetic services and research (policy)
- Reproductive ethics and prevention

Patients offer their:

- genetic and medical data
- ethical perspective
- political and societal influence, etc.

"Sometimes I forgot that I was working with parents instead of colleagues ".
(Prof. Ype Elgersma)

European survey on patient participation



The value of a (genetic) diagnosis

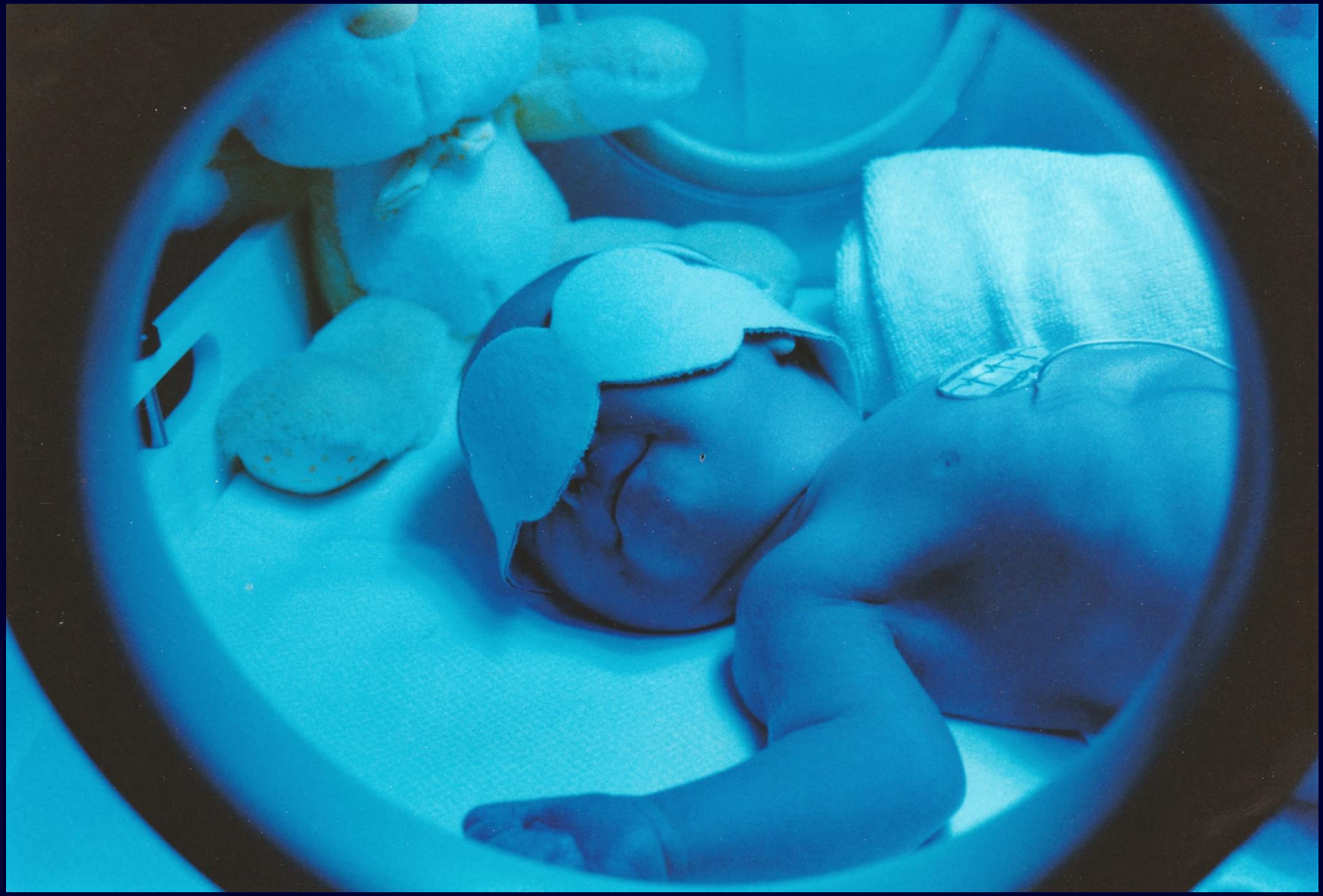
The earlier (the choice to have) a diagnosis, the better:

- preventing diagnostic delay
- access tot research, treatment and/or reimbursement
- avoiding uncertainty, avoiding stigmatisation
- possible relevance for reproductive choices (of family members)

Ethical issues/debate especially concern:

- the reproductive phase (preconception, prenatal)
  - autonomy vs. the well-being of the future/unborn child
- predictive medicine for late onset (genetic) disease
- diagnosis, but no (access to) follow-up
- societal acceptance of, and social care for (preventable) congenital disorders
- definition of ('severe')disease, 'normal', etc.

Martijn, our “unexpected finding”




lijk op vader
dat trekt
nog wel bij
zegt de dokter!

How to deal with (un)expected genetic findings in exome/whole genome (NGS) sequencing?

Always expect the unexpected!

Unexpected findings = incidental findings

Scientific and ethical challenges

- 50.000 -100.000 human genomes sequenced per year in clinic and research
- Relevant unexpected findings in 1% of cases
  - Expected and unexpected data
  - Validated and unvalidated data
  - Different levels of predictively
  - Different context: research, clinic, commercial; adults, children, reproductive, pregnancy, etc.
  - New risk categories

Next-generation sequencing

PERSPECTIVES

APPLICATIONS OF NEXT-GENERATION SEQUENCING — VIEWPOINT

Next-generation sequencing in the clinic: are we ready?

Leslie G. Biesecker, Wylie Burke, Isaac Kohane, Sharon E. Plon and Ron Zimmern

Abstract | We are entering an era in which the cost of clinical whole-genome and targeted sequencing tests is no longer prohibitive to their application. However, currently the infrastructure is not in place to support both the patient and the physicians that encounter the resultant data. Here, we ask five experts to give their opinions on whether clinical data should be treated differently from other medical data, given the potential use of these tests, and on the areas that must be developed to improve patient outcome.

Biesecker et al (2012) Nature Reviews Genetics 13, 818-824

Next-generation sequencing

"We don't want people coming into our clinic for intellectual disability and coming out with a cancer gene; this is not what they came for" (Reis, Nature, April 12, 2012)

Callaway (2012) Nature

nature International weekly journal of science

NATURE | NEWS

Gene hunt is on for mental disability

Pioneering clinical genome-sequencing projects focus on patients with developmental delay.

Ewen Callaway

17 April 2012 | Corrected: 20 April 2012

Medical geneticists are giving genome sequencing its first big test in the clinic by applying it to some of their most baffling cases. By the end of this year, hundreds of children with unexplained forms of intellectual disability and developmental delay will have had their genomes decoded as part of the first large-scale, national clinical sequencing projects.

Exome sequencing could help to identify the causes of intellectual disability in children such as Siebe.

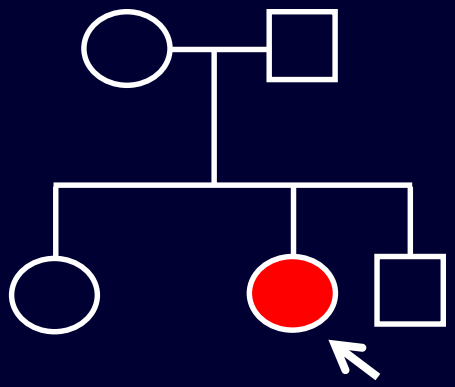
These programmes, which were discussed last month at a rare-diseases conference held at the

Case 2 : unexpected finding after diagnoses for mental retardation

Girl, 10 years old, moderate mental retardation

SNP-array 2010: *de novo* deletion at chromosome 13q (= *BRCA1* region): increased risk at breast and ovary cancer requiring decision making about serious interventions

Case 3: unexpected findings after diagnosis for cancer



Patient with breast cancer participating in genetic research for more personalised medicine

Tumor DNA needs to be genetically compared with DNA from the blood. This may reveal genetic information for other genetic cancers and other genetic disorders that may be relevant for family members.

Consequences for participation in research?

Case 1: unexpected find at prenatal diagnoses

Prenatal diagnostics because of women's age
Outcome: 47, XYY

Most 47,XYY clinically normal

Older literature: more 47,XYY in prison

Recent literature: more behavioural problems and learning problems, but especially in determined by socio-economic circumstances

Assent

Feedback and informed consent... how?!

Informed consent

Opt-out

Broad consent

Blanket consent

Tiered consent

Generic consent

Opt-in

Restrictive feedback (no, unless) vs. Qualified feedback (yes, if)

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   soep met garnalen en chinese champignons
7. Sun La Tong ..... € 3,80
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13. Pisang Goreng ..... € 3,20
   gebakken banaan, 6 stuks
14. Kroepoek ..... € 2,10
15. Cassave Kroepoek ..... € 2,70
16. Saté Ajam, kipfilet 4 stokjes met pindasaus ..... € 4,60
17. Saté Oedang, gamalen 3 stokjes met pindasaus ..... € 8,30
17a. Gebraden halve kip met pikante saus ..... € 4,20
17b. Sausen (pikante, pinda of zoetzure saus) ..... € 1,90
17c. Witte rijst ..... € 2,30

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20. Foe Yong Hai met Chinese garnalen ..... € 12,30
21. Foe Yong Hai met kreeft ..... € 12,30

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22. Tjap Tjoy met varkenshaas ..... € 8,50
23. Tjap Tjoy met kipfilet en knapperig gebraden kip erbovenop ..... € 9,90
24. Tjap Tjoy met gesneden ossenhaas ..... € 12,30
25. Tjap Tjoy met Chinese garnalen ..... € 13,10

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27. Ma Po Tofu ..... € 12,30
   Tofu blokjes met fijngesneden varkensvlees en groenten in Ma Po Saus
28. Ka Hong Tofu ..... € 11,00
   gebakken Tofu met varkenshaas, Chinese champignons en groenten
29. Tofu in sambalsaus ..... € 10,50
   Gebakken Tofu met varkenshaas en groenten

CHINESE MIX SCHOTELS

30. Hao You San Xin ..... € 14,40
   kip, garnalen en ossenhaas in oestersaus
31. Tofu Bao ..... € 13,30
   Tofu, kip, garnalen en Cha Sieuw
32. Tjap Ap Bao ..... € 14,40
   for nam, Cha Sieuw en Peking eend met pikante saus
33. Pi Kam Sam Xin ..... € 14,40
   Chinese garnalen, kip, ossenhaas, varkenshaas met pikante tomatensaus

OSSENHAASGERECHTEN

34. Shanghai Paksoi ..... € 15,30
   gesneden ossenhaas met Chinese groenten
35. Po Lo Ngau ..... € 15,30
   gesneden ossenhaas met ananas in zoetzure saus
36. Kun Chong Ngau ..... € 15,30
   gesneden ossenhaas met verse gember en lente-uitjes
37. Tausi Ngau ..... € 15,30
   gesneden ossenhaas met zwarte sojabonensaus
38. Yeng Chong Ngau ..... € 15,30
   gesneden ossenhaas met uien en verse tomaat
39. Ton Ko Ngau ..... € 15,30
   gesneden ossenhaas met Chinese champignons
40. Ossenhaas met champignons ..... € 15,30
41. Ossenhaas met kerriesaus ..... € 15,30
41a. Hui Kuo Ngau ..... € 15,50
   gesneden ossenhaas in Si-chuan (pittige) saus

VARKENSHAASGERECHTEN

42. Cha Sieuw ..... € 13,60
   in honing gemarineerde varkenshaas
43. For Nam ..... € 13,60
   geroosterd speenvarken met pikante saus
44. Lychee Yuk ..... € 12,80
   varkenshaas met lychees in zoetzure saus
45. Yu Siang Lo Shi ..... € 13,80
   fijn gesneden varkenshaas met een pittig gekruiden saus
46. Kei Lan Yuk ..... € 12,00
   varkenhaas met broccoli
47. Hui Kuo Lo Shi ..... € 13,80
   fijn gesneden varkenshaas met pittige Si-chuansaus
48. Ton Ko Yuk ..... € 13,60
   gesneden varkenshaas met Chinese champignons
49. Ku Lo Yuk ..... € 11,30
   gepaneerde varkenshaas met vruchten en zoetzure saus
49a Ku Lo Yuk ..... € 11,30
   gepaneerde vleesballetjes met zoetzure saus
50. Gesneden varkenshaas met kerriesaus ..... € 11,00
52. Gesneden varkenshaas met champignons ..... € 11,00
53. Gesneden varkenshaas met Roedjaksaus ..... € 11,00

54. Babi Pangang in pikante saus ..... € 11,00
54a. Babi Pangang in pikante saus met ananas ..... € 11,00
55. Babi Pangang in kerriesaus ..... € 11,00
56. Babi Pangang in ketjapsaus ..... € 11,00
57. Babi Pangang in pindasaus ..... € 11,00
58. Babi Pangang in Roedjaksaus ..... € 11,30
   Indisch gekruide saus

KIPGERECHTEN

59. Dan Zhi Kai ..... € 12,30
   licht gepaneerde kipfilet met zoetzure saus
60. Gon Bao Kai ..... € 12,50
   gesn. kipfilet met cashewnoten in pittige saus
61. Ton Ko Kai ..... € 12,50
   gesn. kipfilet met Chinese champignons
62. Tausi Kai ..... € 12,00
   gesneden kipfilet met zwarte sojabonensaus
63. Gesneden kipfilet met kerriesaus ..... € 12,00
64. Gesneden kipfilet met champignons ..... € 12,00
64a. Jiao yan Kai ..... € 12,30
   kipfilet gekruid met knoflook en peper
64b. Po Lo Kai ..... € 12,00
   gesneden kipfilet met ananas en zoetzure saus
64c. Ku Lo Kai ..... € 12,00
   Kippenballetjes met zoetzure saus

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- Mini Loempia's
- Cassave Kroepoek
- Babi Pangang
- Kipfilet met Ananas
- Koe Loe Yuk
  Deegbolletjes met varkenshaas
- Foe Yong Hai
  Bekend Chinees omelet gerecht
- Witte Rijst / Nasi / Bami

Catering B

€ 10,80 per persoon

- Saté Ayam
- Cassave Kroepoek
- Mini Loempia's & Kerrie Ko
- Pansit & Gebakken Banaan
- Babi Pangang
- Tjap Tjoy
- Foe Yong Hai
- Koe Loe Yuk
  Deegbolletjes met varkenshaas
- Kipfilet in Ketjapsaus
- Daging Roedjak *(Ind. Rundvlees)*
- Witte Rijst / Nasi / Bami

Catering C

€ 12,80 per persoon

- Saté Ayam
- Cassave Kroepoek
- Cha Siu Mai & Gebakken Banaan
- Mini Loempia's & Kerrie Ko
- Babi Pangang & Cha Siew
- Foe Yong Hai & Koe Loe Kai
- Varkenshaas in Kerrie saus
- Kipfilet met Cashewnoten
- Gon Bao Niu Yuk
  Ossenhaas in Gon Bao suas
- Tja Jing Yu Pin
  Droog Gebakken Tongfilet met pepersmaak
- *Witte Rijst / Nasi / Bami*

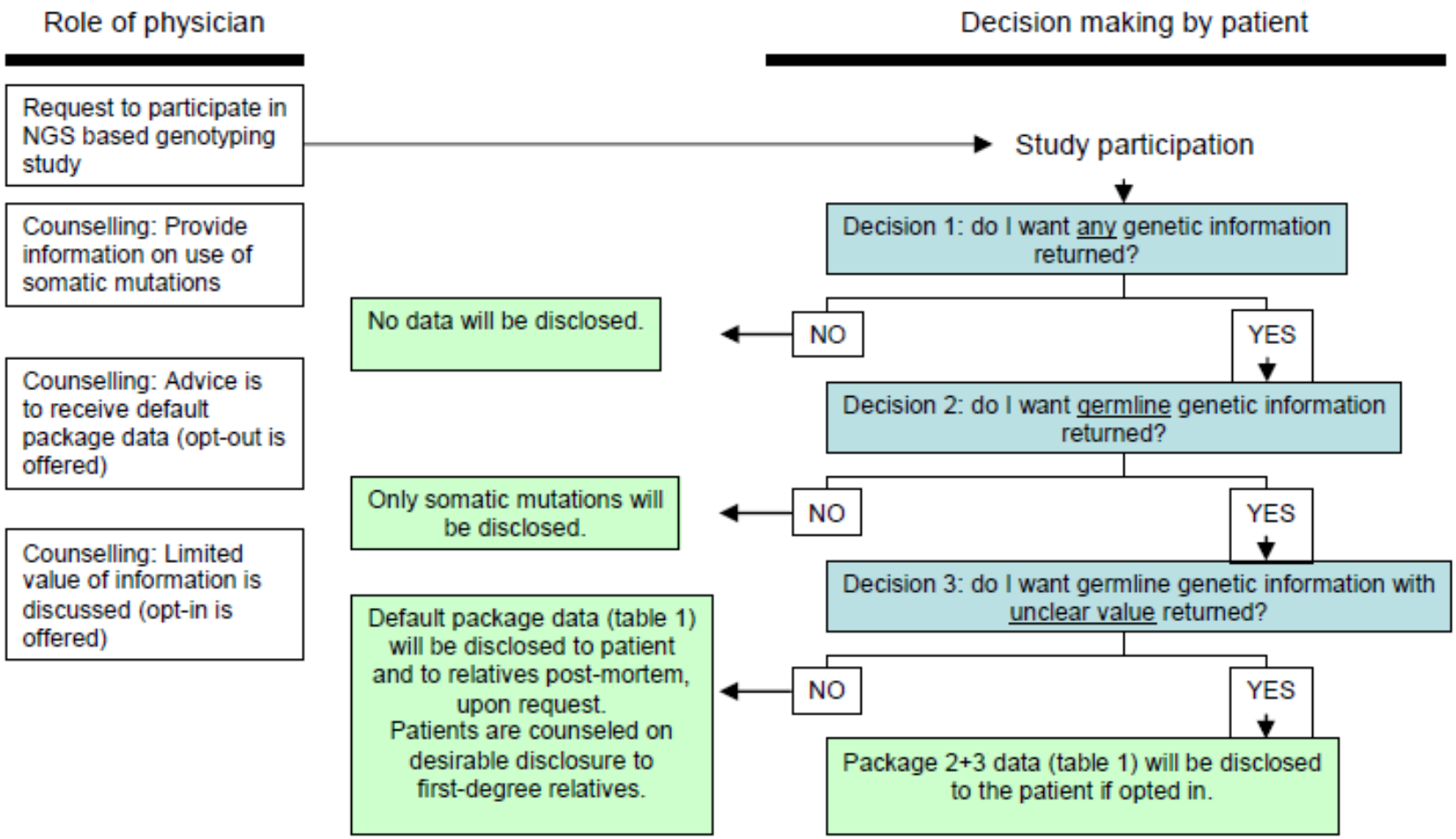
Package	Content	Opt-in/ opt-out	Moral justification	When to offer?
Default package	Life-saving data and data of immediate clinical utility	Opt-out system	Beneficence Autonomy (positive account)	Always
Additional package #1	Data of potential or moderate clinical utility	Opt-in system	Autonomy (negative account)	Context-specific
Additional package #2	Data of reproductive significance	Opt-in system	Autonomy (negative account)	Context-specific
Additional package #3	Data of personal or recreational significance	Opt-in system	Autonomy (negative account)	Context-specific

Bredenoord et al, Hum Mutat, 2011

Lolkema et al (2013) J Clin Oncology

Figure 1: Return of Genetic Results in Oncology: Patient oriented flow chart on tiered consent

Figure 1



American College of Medical Genetics and Genomics

- Policy application statement: Points to consider in the clinical application of genomic sequencing (May 2012)
- Recommendations for reporting of incidental findings in clinical exome and genome sequencing (March 2013)

ACMG recommendations: a revolution!

" ….. when a report is issued for clinically indicated exome and genome sequencing, a minimum list of conditions, genes and variants should be routinely evaluated and reported to the ordering clinician who can place them into the context of that patient's medical and family history, physical examination and other laboratory testing. We have recommended that these findings be reported without seeking preferences from the patient and family and without limitation due to the patient's age."

ACMG: Minimum list of genetic disorders to be reported

Hereditary Breast and Ovarian Cancer; Li-Fraumeni Syndrome; Peutz-Jeghers Syndrome; Lynch Syndrome; Familial adenomatous polyposis; MYH-Associated Polyposis; Adenomas, multiple colorectal, FAP type 2; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas; Von Hippel Lindau syndrome; Multiple Endocrine Neoplasia Type 1; Multiple Endocrine Neoplasia Type 2; Familial Medullary Thyroid Cancer (FMTC); Hamartoma Tumor Syndrome; Retinoblastoma; Hereditary Paraganglioma-Pheochromocytoma Syndrome; Tuberous Sclerosis Complex; WT1-related Wilms tumor; Neurofibromatosis type 2; Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms and Dissections; Hypertrophic cardiomyopathy, Dilated cardiomyopathy; Catecholaminergic polymorphic ventricular tachycardia; Arrhythmogenic right ventricular cardiomyopathy; Romano-Ward Long QT, Syndromes Types 1, 2, and 3, Brugada Syndrome; Familial hypercholesterolemia; Malignant hyperthermia susceptibility

ACMG Recommendations & Newborn screening

- “these recommendations address incidental findings sought and reported during clinical sequencing for a specific clinical indication but do not address preconception sequencing, prenatal sequencing, newborn sequencing or sequencing of healthy children and adults.”

- “Conditions that were part of routine newborn screening were excluded as they have their own assessment criteria and are applied in a specific public health framework.”

What about Europe?

European Workshop on Genetic Testing Offer in Europe

- A ‘red list’ of genes and/or variants that disclose ‘high risk’ and potentially treatable genetic predisposition would be helpful to deal with incidental findings in practice. There is a consensus that, at this stage, there is no meaningful clinical use of low risk predictions and hence, these should in principle not be communicated to the patient. It is an aspect of consumer protection to warn the community against unnecessary medicalization.

- An informed consent is necessary for a genomic diagnostic approach. It should allow the patient to decide beforehand whether or not to receive information other than that related to the disease under investigation.

- Opinions and regulations vary as to whether a clinician can overrule the patient’s or parents opinion in case of severe risk alleles, e.g. highly penetrant cancer predisposition mutations.

Different rules for research?

- Should we keep the distinction between research and clinic (screening/diagnostics)?
  - No: Research laboratories not certified for diagnostics
  - Yes: Otherwise, the researcher may have knowledge about the patient, the patient does not have

TAKING IT TO THE BioBANK

By Catherine Harris

Four positions for debate

1. It is a fundamental patients' right to have the choice to access his/here genetic data and genetic information as part of any (medical/research) record

2. AGCM recommendations: Europe should follow

3. Incidental findings with 'life relevance': no distinction between research, screening or diagnostics ('life relevance' includes medical and reproductive relevance, and quality of life)

4. No principal objections exists to apply exome/genome sequencing for neonatal screening

Contact & websites

- c.oosterwijk@vsop.nl

  - www.vsop.nl
  - www.egan.eu
  - www.biomedinvo4all.com
  - www.gencodys.eu
  - www.grip-netwerk.eu
  - www.patientpartner-europe.eu
  - www.patientsacademy.eu
  - www.preparingforlife.org