Webinars # 10

Incidental and secondary findings from exome/genome sequencing

***

views of various European countries and ESHG

Chaired by Pr Laurence Faivre,

CHU Dijon-Bourgogne, Dijon, France - Chair WP T&E

Tuesday 28 November from 5pm to 6.30 pm French time

European Commission

EUROPEAN REFERENCE NETWORKS

Helping patients with rare or low-prevalence complex diseases

European Reference Networks ITHACA

Welcome – Technical points

Thank you for joining us today, we are please to be numerous

This Webinar is being recorded, please let us know if you do not wish to be registered

➔ Few technical points to make this webinar a success

- Turn off your microphone and disconnect your camera

➔ Questions and discussions time at the end of the presentations

- prefer to use the chat
- raise your hand at the time of the questions
- we will try to answer the questions sent in the registration form

➔A satisfaction survey

➔Webinars # will be available on ITHACA's Website (recording + PPT)

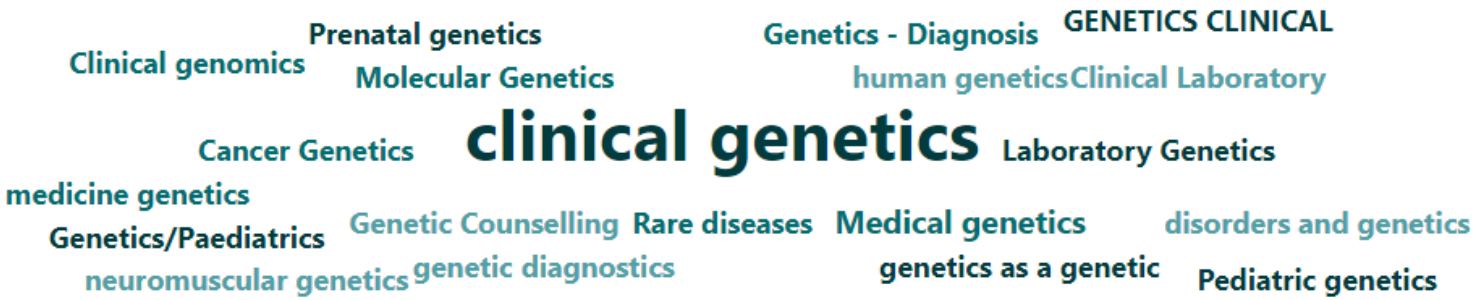
- https://ern-ithaca.eu/documentation/educational-resources/

Contact : Anne Hugon Project Manager ERN ITHACA - anne.hugon@aphp.fr

Survey registration feed back

- We are please to be numerous 446 registrations (real 420)
  - ~ 90 Patient Organisations
  - Ithaca's members
  - > 20 countries

- Field of Interest



- What is the situation like in your country?

Having noted that many countries outside Europe are connected this evening, we propose to organise a new webinar and ask for your participation to tell us how things are going in your countries. This will enable us to expand and share our knowledge beyond Europe.

Belgium
Croatia
Cyprus
France
Greece
Hong Kong
Iraq
Irish
Italy
Lithuania
Morocco
Northern Ireland
Poland
Romania
Scotland
Spain
Switzerland
Turkey
United Kingdom
USA

Welcome and Introduction

- Pr Laurence Faivre
- The issue of incidental data, which has always existed in genetics, is becoming exponential with the advent of genomic medicine. The issue of secondary data, involving an active search for variants in a list of so-called actionable genes, is very popular in the USA, whereas Europeans are urging caution.

- In this webinar, we would like to take a look at the evolution of recommendations made by certain European countries, as well as those of the ESHG.

Agenda

Welcome and Introduction

- Speaker : Pr Laurence Faivre
- From : CHU Dijon-Bourgogne, Dijon, France

1. ESHG recommendations on Opportunistic genomic screening (15mn)

- Speaker : Dr Francesca Forzano
- From : King's College, London, UK

2. Secondary findings in exome sequencing. Experience in a tertiary public hospital in Spain (15mn)

- Speaker : Dr Marta Codina Solà and Dr Anna Abuli
- From : Hospital Universitari Vall d'Hebron, Barcelona, Spain

3. Management of unexpected findings in the NHS England Genomic Medicine Service (15mn)

- Speaker : Mrs Rachael Mein
- From : NHS England Genomics Unit Senior Laboratory Advisor (Rare Disease),UK

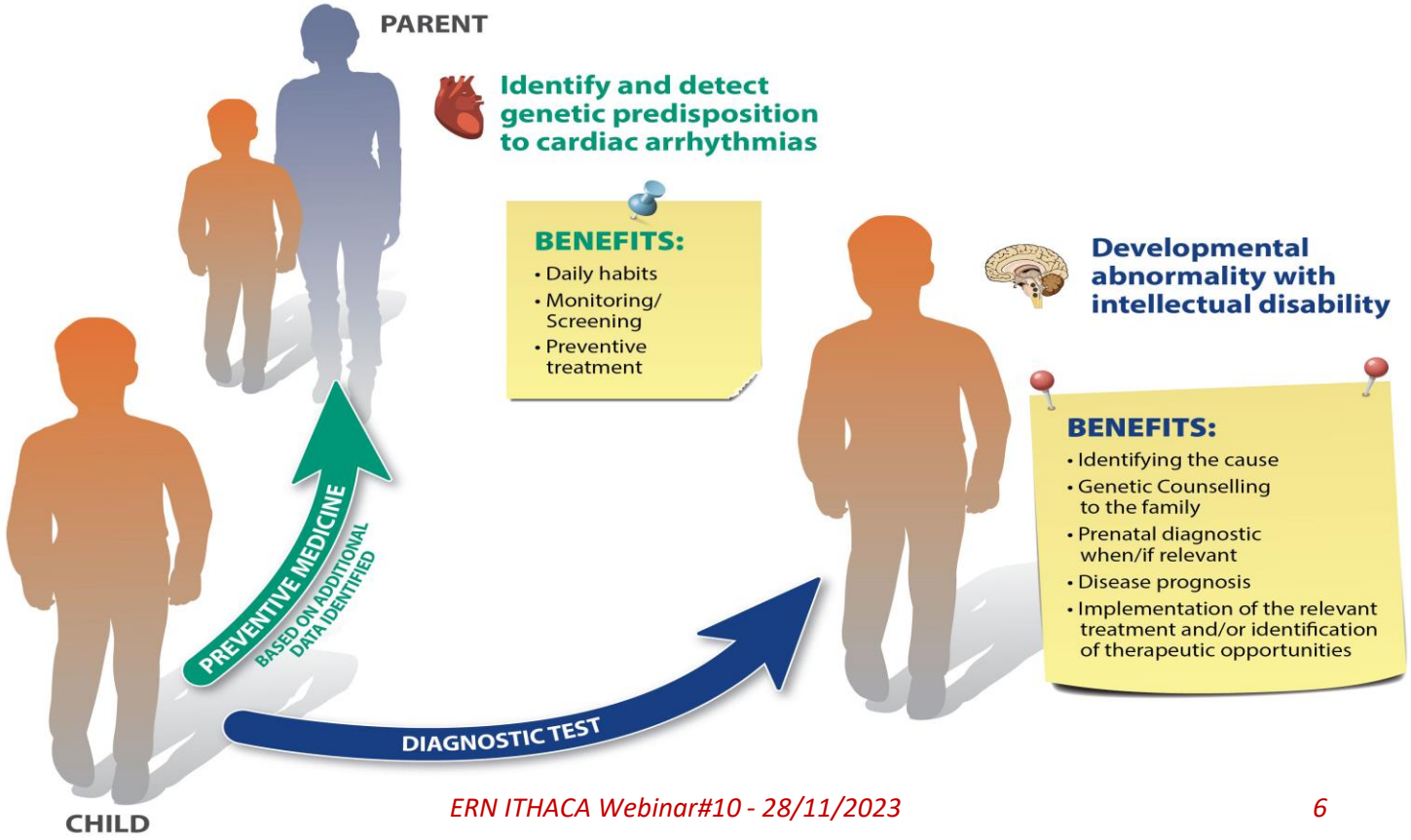
4. Studies for exploring the expectations of patients/families regarding additional findings from exome sequencing in France (15mn)

- Speaker : Pr Laurence Faivre
- From : CHU Dijon-Bourgogne, Dijon, France

• Conclusion with speakers and moderator (~20 mn)

Introduction

- ES/GS: powerful tool for diagnosis of rare and heterogeneous diseases, but increase risk of additional information, unrelated to the symptoms that justified the prescription of the test



Introduction

- Difference between:
  - Incidental/unexpected findings: discovered unintentionally
  - Secondary findings: the patient is offered to have results from a list of actionable diseases if they so wish, since the test allows it

- They may be of potential interest to patients/families for prevention/ treatment, but may also lead to psychological distress

- Some foreign learned societies recommend that the patient be offered a systematic analysis of a pre-established list of so-called "actionable" genes (USA in particular), while others do not recommend this analysis in the absence of clear arguments about the benefit-risk ratio

ESHG recommendations on Opportunistic genomic screening

Speaker : Dr Francesca Forzano
From : Guy’s and St Thomas NHS Foundation Trust and King's College, London, UK

Outline

1. Rationale for ESHG Recommendations
2. What is Opportunistic Genomic Screening (OGS)? –definition
3. Process
4. ESHG Recommendations on OGS

Note: we focused on **diagnostic** and not on research

Rationale : existing confusions

- **WGS in health care: recommendations of the ESHG. van El CG et al. EJHG May 16th 2013** doi: 10.1038/ejhg.2013.46 ***vs*** **ACMG Recommendations for Reporting of IF Green R at al. GM June 20th 2013** doi: 10.1038/gim.2013.73
- Definitions
- Inconsistencies in applications and regulations
- Legal obligations
- External Quality Assessments
- Need for harmonization

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OGS: definitions and conceptual clarification

- **Primary finding (PF):** variants actively looked for that are related to the original, targeted indication for testing
- **Incidental finding (IF):** results unrelated to the original reason for testing, which were not actively looked for
- **Unsolicited finding (UF):** a synonym of Incidental Findings, which we believe is a more appropriate definition (van El, Cornel et al. 2013)
- **Secondary finding (SF):** variants actively looked for that, although not related to the original indication for testing, may be relevant for the health prospects and/or reproductive choices of the patient or the patient's family. May also be termed "additional sought findings".
- **Actionable finding (AF):** variants in genes which have direct, significant impact for the medical care of the patient and likely family members, including treatment and prevention
- **Opportunistic Genomic Screening (OGS):** to refer to the active or deliberate search for SFs in genomic medicine

ESHG Procedures to draft Recommendations

1. Proposals of topic – PPPC members, ESHG exec, ESHG Board, membership
2. Preparation of draft – PPPC working group /+ other Committees /+ expert collaborators
3. Review of draft – PPPC members / other Committees members
4. Publication on ESHG website for membership review and comments (1 month) Possibility to invite experts to pre-peer review
5. Integration of comments
6. Submission to ESHG Full Board for review and endorsement (1 month)
7. Submission to EJHG for peer review and publication

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European countries: 51

National Human Genetic Societies: 51

EU member countries: 27

Sources Wikipedia; https://www.eshg.org/index.php?id=76

European Journal of Human Genetics (2021) 29:365–377
https://doi.org/10.1038/s41431-020-00758-w

POLICY

Opportunistic genomic screening. Recommendations of the European Society of Human Genetics

Guido de Wert[1] · Wybo Dondorp[1] · Angus Clarke[2] · Elisabeth M. C. Dequeker[3] · Christophe Cordier[4] · Zandra Deans[5] · Carla G. van El[6] · Florence Fellmann[7] · Ros Hastings[8] · Sabine Hentze[9] · Heidi Howard[10,11] · Milan Macek[12] · Alvaro Mendes[13] · Chris Patch[14,15] · Emmanuelle Rial-Sebbag[16] · Vigdis Stefansdottir[17] · Martina C. Cornel[7] · Francesca Forzano[18] · On behalf of the European Society of Human Genetics

Eur J Hum Genet **29**, 365–377 (2021). https://doi.org/10.1038/s41431-020-00758-w

OGS is a form of screening

Performing a broader analysis amounts to a form of screening, for which **the general framework of screening criteria is applicable**.

Ethical principles of proportionality, respect for autonomy, justice should be considered.

In light of the non-indicated nature of OGS, **there is a strong burden of proof** that such screening is on balance beneficial for those to whom it is offered.






Limitations

- Lack of conclusive evidence that OGS can **alter the natural history of disease** in a significant proportion of those screened
- Actionability is **contextual**
- Actionability depends on **penetrance and expressivity** of variants > can be reduced/unknown in general population > potential iatrogenic harm, distress
- Adds-on **costs and resources** of the process not adequately explored

OGS is not a standard of care

ESHG continues to recommend a generally cautious approach.

It is too early to recommend OGS as part of the professional standard of care.

Any OGS should be embedded in **adequate pilot and evaluation studies**.

Clear procedures and criteria are needed for composition and extension of the **list** of genetic variants included - a wider debate, involving all relevant stakeholders, especially patients, is of utmost importance. Selection should consider:

1. Variants: well-known, highly penetrant
2. Genetic disorders : adequately and effectively prevented and/or treated.
3. Context : penetrance of particular variants in a given population, capacity of health care systems
4. Psychological impact, actual patient empowerment
5. Counseling needs

Informed Consent : Opt-in only

Informed consent should be a central ethical norm in the framework of screening.

Alternatives such as opting out or a coercive offer of OGS are problematic.

A dynamic consent approach may be helpful but needs further empirical study.

The patient's right not to know should be respected as far as reasonably possible, while allowing professionals to still inform the patient about IF of great importance for the patient's or their close relatives' health

The **provisional nature** of current knowledge on penetrance in unaffected population and families should be addressed as well as potential crossovers with research and options for recontacting in case new scientific evidence of clinical relevance arises.

OGS as one of potential options

Depending on **developing evidence** on penetrance and actionability, but also taking account of the **resources** available for health care in European countries, OGS pilots may be justified to generate data for a future, informed, comparative analysis of OGS and its main alternatives, namely (the offer of) **universal genomic screening** for highly penetrant, actionable variants, and (more systematic) **cascade testing** in relatives of probands affected with (avoidable) diseases caused by highly penetrant genetic variants.

OGS in minors

☑ PGx variants and variants leading to early-onset actionable conditions.

☑ late-onset disorders in minors who are not expected to become competent later if such targeted OGS would meet the principles of proportionality and justice

⛔ variants leading to later-onset actionable conditions

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ACMG Secondary Findings (SF) vs ESHG Opportunistic Genomic Screening (OGS)

ITEM	ACMG American College of Medical Genetics and Genomics	ESHG The European Society of Human Genetics
Normative framework	Diagnostic	Screening
SF/OGS in all ES/GS, diagnostic	☑ DO	⛔ DON'T
SF/OGS in all ES/GS, research	⛔ ACMG policy for clinical testing	⛔ DON'T as standard ☑ OGS in ad hoc pilots/research to accrue data
List of genes/variants	☑ ACMG SF list	⛔ NO list ☑ List contextual to pilots
SF/OGS in minors	☑ DO	⛔ DON'T ☑ EXCEPTIONS early-onset actionable PGx variants Conditionally for minors who will be incompetent adults
Patient's choice	**Opt-out**	**Opt-in only**

Members of the ESHG Exec

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Prof. Maurizio Genuardi (Rome, Italy) President-Elect
Prof. Gunnar Houge (Bergen, Norway) Vice-President
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2019/2020

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Markus Perola (Helsinki, Finland)
Dragica Radojkovic (Belgrade, Serbia)
Emmanuelle Rial-Sebbag (Toulouse, France)
Vigdis Stefánsdottir (Reykjavik, Iceland)

Secondary findings in exome sequencing. Experience in a tertiary public hospital in Spain

Speaker : Dr Marta Codina Solà and Dr Anna Abulí
From : Hospital Universitari Vall d'Hebron, Barcelona, Spain

The University Hospital Vall d'Hebron

VHIR

The University Hospital Vall d'Hebron is one of the biggest hospitals of Spain.

It offers tertiary-level healthcare for infant and adult patients.

1952 | Inaugurated in Barcelona

Nowadays it is the Public Centre with more activity in healthcare and research in Catalonia.

- **Pediatrics, gynecology and obstetrics**
- **General (Adults)**
- **Research**

Vall d'Hebron Hospital

Vall d'Hebron Barcelona Campus Hospitalari

Vall d'Hebron Institut de Recerca

Department of Clinical and Molecular Genetics, Vall d'Hebron Hospital, Barcelona

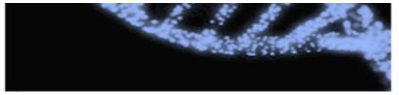
Medical Genetics

⟺

Genetic Counselling

⟺

Molecular Genetics



ES - Research Project
ENOD

2016

Periodic Reanalysis

2019

GS - Research Project
IMPACT

2023

2018
ES
Clinical Practice

2021

Retrospective evaluation

ARTICLE

Check for updates

An spanish study of secondary findings in families affected with mendelian disorders: choices, prevalence and family history

Marta Codina-Solà[1,2,3]✉, Laura Trujillano[1,2,4], Anna Abulí[1,2,3], Eulàlia Rovira-Moreno[1,2,3], Patricia Muñoz-Cabello[1,2], Berta Campos[1,2], Paula Fernández-Álvarez[1,2,3], Dolors Palau[1], Estela Carrasco[5,6], Irene Valenzuela[1,2,3], Anna Maria. Cueto-González[1,2], Amaia Lasa-Aranzasti[1,2,3], Javier Limeres[7,8,9], Jordi Leno-Colorado[1,2], Mar Costa-Roger[1,2], Alejandro Moles-Fernández[1,2], Judith Balmaña[5,6], Orland Díez[2,5], Ivon Cuscó[1,2,3,4,11], Elena Garcia-Arumí[1,2,3,4,10] and Eduardo Fidel Tizzano[1,2,3]

- Retrospective study including **824 families** who underwent singleton WES between 2016 and 2021.
- All families received **extensive genetic counselling** by a qualified professional (medical geneticist or genetic counsellor).
- All participants were offered to **receive SFs as defined in the ACMG recommendations v2 (59 genes).**
- Consent was provided by both parents or a legal representative if the patient was a minor under 16 years or if they were over 16 years but incapable of providing consent for themselves.

European Journal of Human Genetics volume 31, pages 225–230 (2023)

RESULTS: CHOICES

- Overall acceptance of **90%**
- Previous studies: 76% to 93.5%

Table 1. Summary of previous studies exploring participant's preferences for SFs.

Authors, ref.	Participants (*n*)	Site	Age of participants	Categories of SF	Setting
Shahmirzadi et al. [7]	200	USA/ Canada	Adults, children	Four categories of SFs defined accordingly to age of onset of the disease and reproductive accionability	Clinical
Regier et al. [8]	1200	Canada	Adults	Discrete choice questionnaire evaluating 5 attributes (penetrance, treatability, severity of the disease, carrier status and cost of receiving the results	Research
Fiallos et al. [9]	790	USA	Adults, children	ACMG v1	Research
Wynn et al. [22]	219	USA	Adults	11 types of genetic results with different degree of risk; availability and effectiveness of screening, prevention and treatment and acceptability of screening, prevention and treatment	Research
Rini et al. [11]	152	USA	Adults	Six categories of SFs with low medical actionability	Research
Similuk et al. [12]	66	USA	Adults, children	ACMG v2	Research
Swanson et al. [35]	685	USA	Children, prenatal	ACMG v2	Clinical
Horiuchi et al. [14]	2480	Japan	Adults, children	ACMG v2	Research
Rego et al. [15]	150	USA	Children, prenatal	Hypotethical categories of SFs dfined according to severity of the disease, availability of treatment, reproductive utility and age of onset.	Research
This study	824	Spain	Children, adult, prenatal	ACMG v2	Clinical

RESULTS: CHOICES

Correlation with clinical and demographic factors:

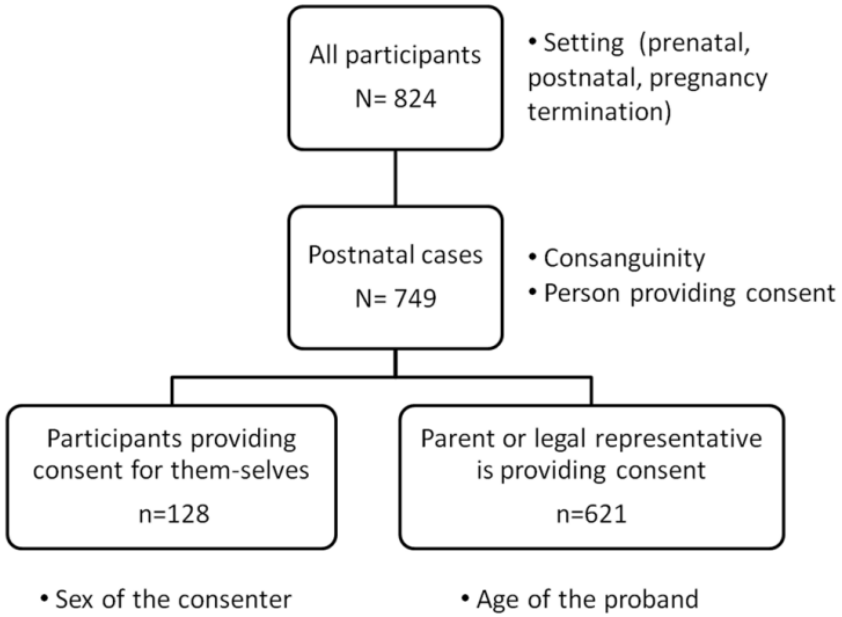


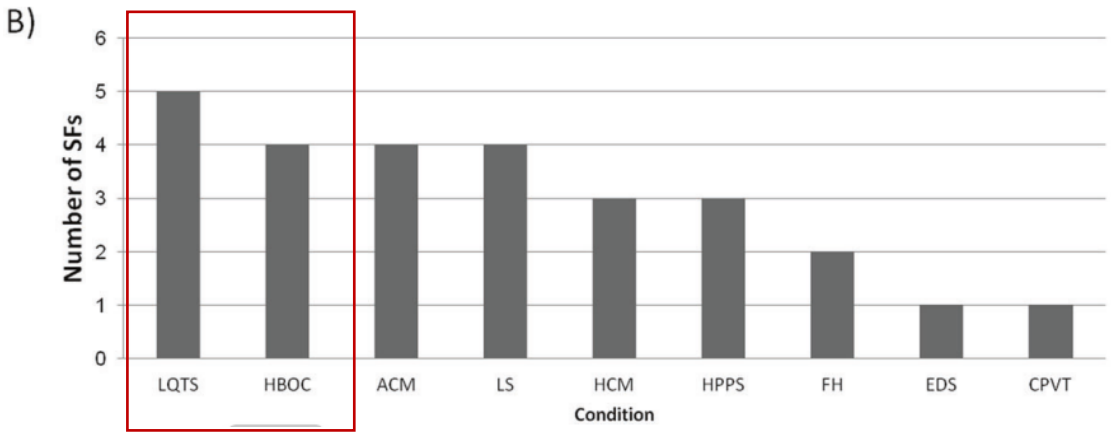
Table 2. Factors influencing choice of receiving SFs.

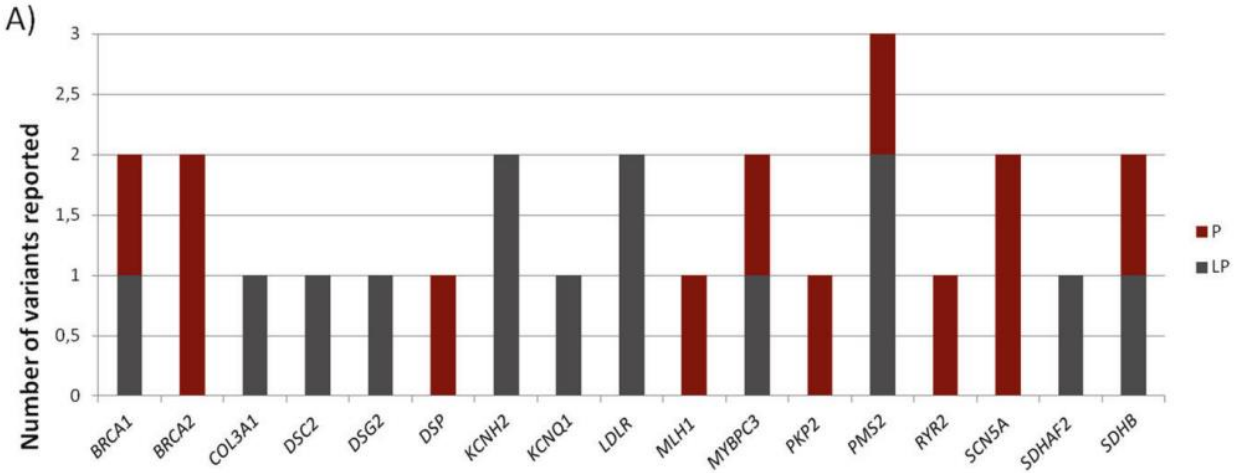
Variable		# (%)	Choice of SF		*P* value
			No (%)	Yes (%)	(FET)
Setting	Prenatal	20 (2%)	6 (30%)	14 (70%)	0.03
	Postnatal	749 (91%)	72 (10%)	677 (90%	
	Pregnancy termination	55 (7%)	6 (11%)	49 (89%)	
Person providing consent[a]	Parent or legal representative	621 (83%)	60 (10%)	561 (90%)	0.68
	Self	128 (17%)	12 (9%)	116 (91%)	
Consanguinity[a]	Yes	63 (8%)	12 (19%)	51 (81%)	0.01
	No	686 (92%)	60 (9%)	626 (91%)	
Sex of the consenter[b]	Female	81 (63%)	3 (4%)	78 (96%)	0.01
	Male	47 (37%)	9 (19%)	38 (81%)	
Age of the proband when another is providing consent[c]	Minor (<=16)	556 (90%)	59 (11%)	497 (89%)	0.01
	Adult (>16)	65 (10%)	1 (2%)	64 (98%)	

P values were calculated using Fisher's Exact Test (FET).
[a]This analysis includes only postnatal cases.
[b]This analysis includes only postnatal cases and participants providing consent for one-self.
[c]This analysis includes only postnatal cases and cases for which a parent or legal representative is providing consent. See Fig. 1 for a general scheme of the analysis performed.

RESULTS: PREVALENCE

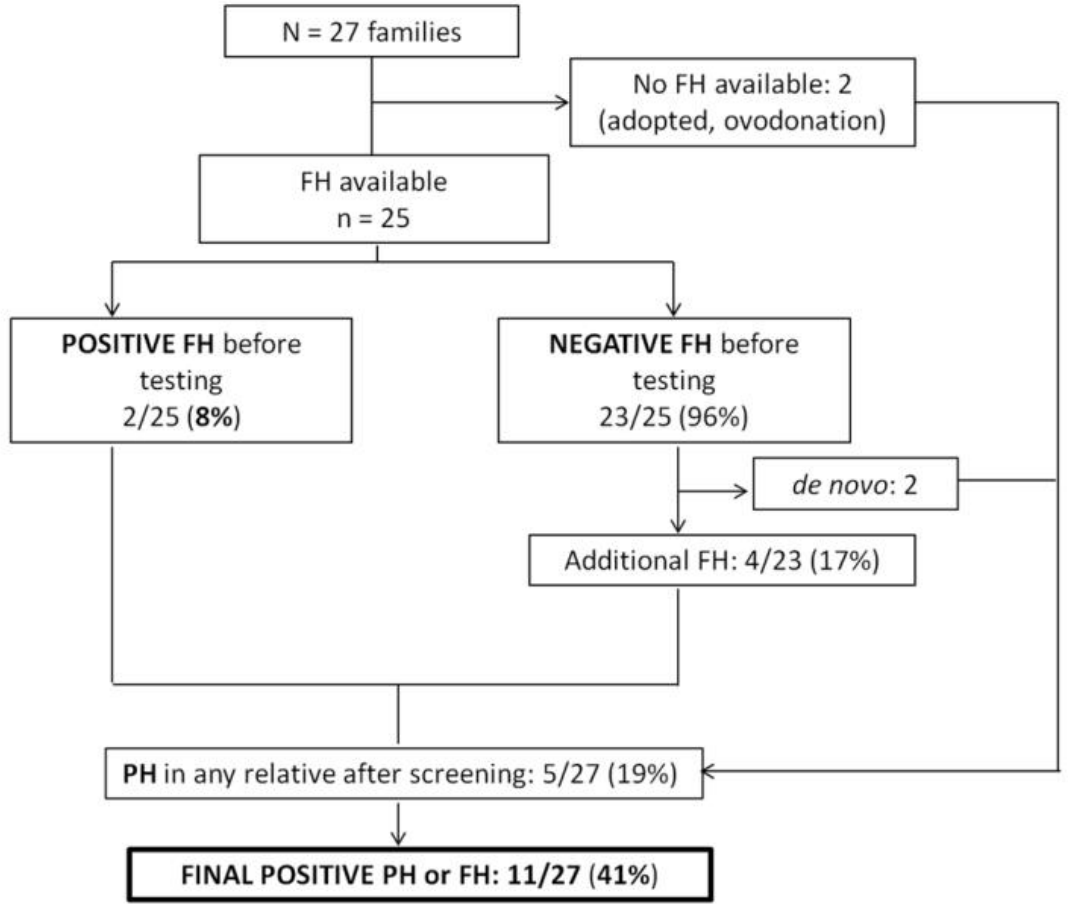
- Based on the **740** probands who underwent genome (n = 4) or exome sequencing (n = 736) and consented to SF.
- All variants reviewed by MTD (6 pre-selected variants downgraded to VOUS).
- 27 pathogenic or likely pathogenic variants were identified in 27 individuals.
- **SF prevalence of 3.6%.**





RESULTS: FAMILY HISTORY

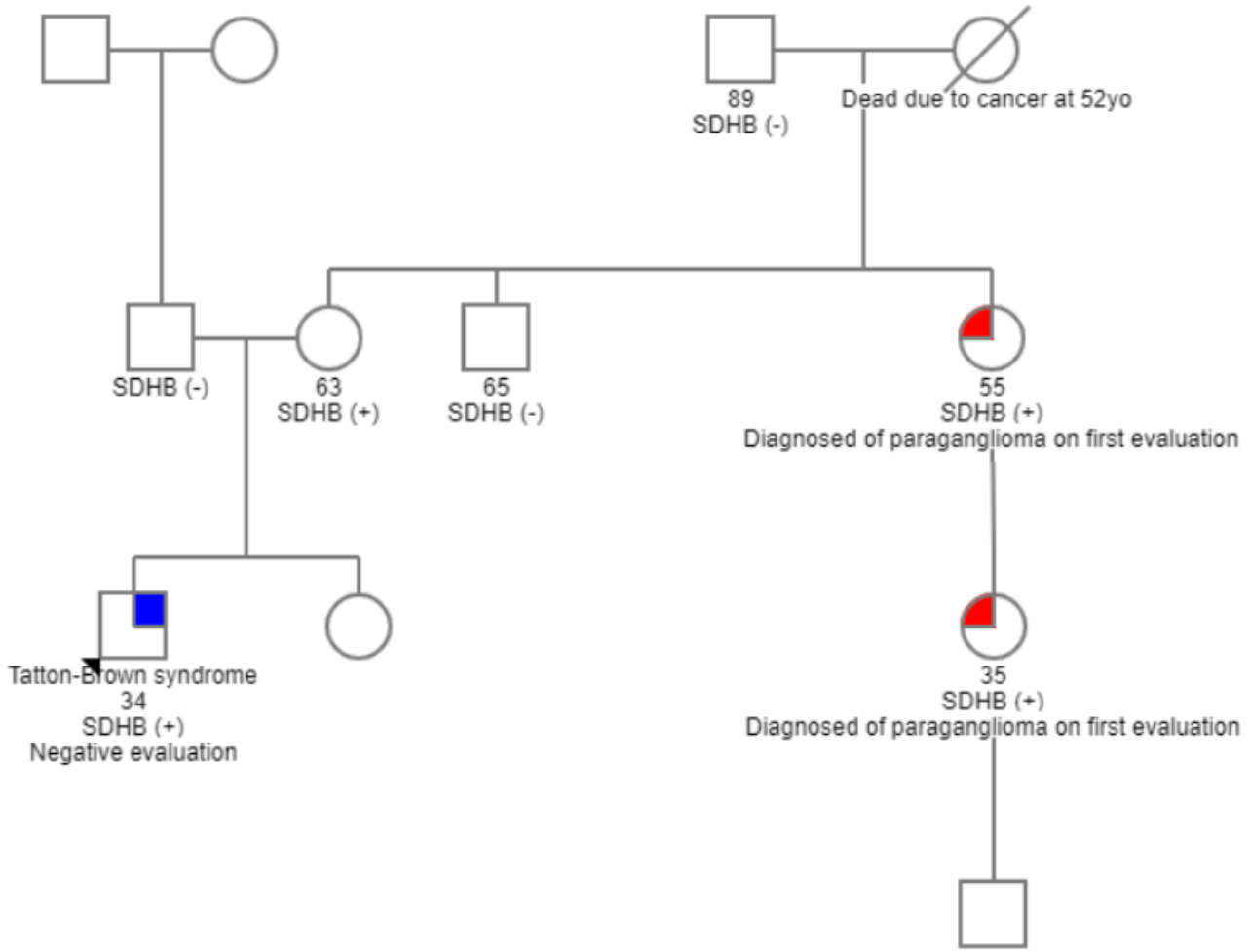
- Genetic testing was offered to at-risk relatives, according to current recommendations.
- SF disclosure resulted in a mean of 2.7 direct studies per family, with a total of 73 genetic studies being performed.
- Follow-up time: at least 1 year after the SF disclosure.



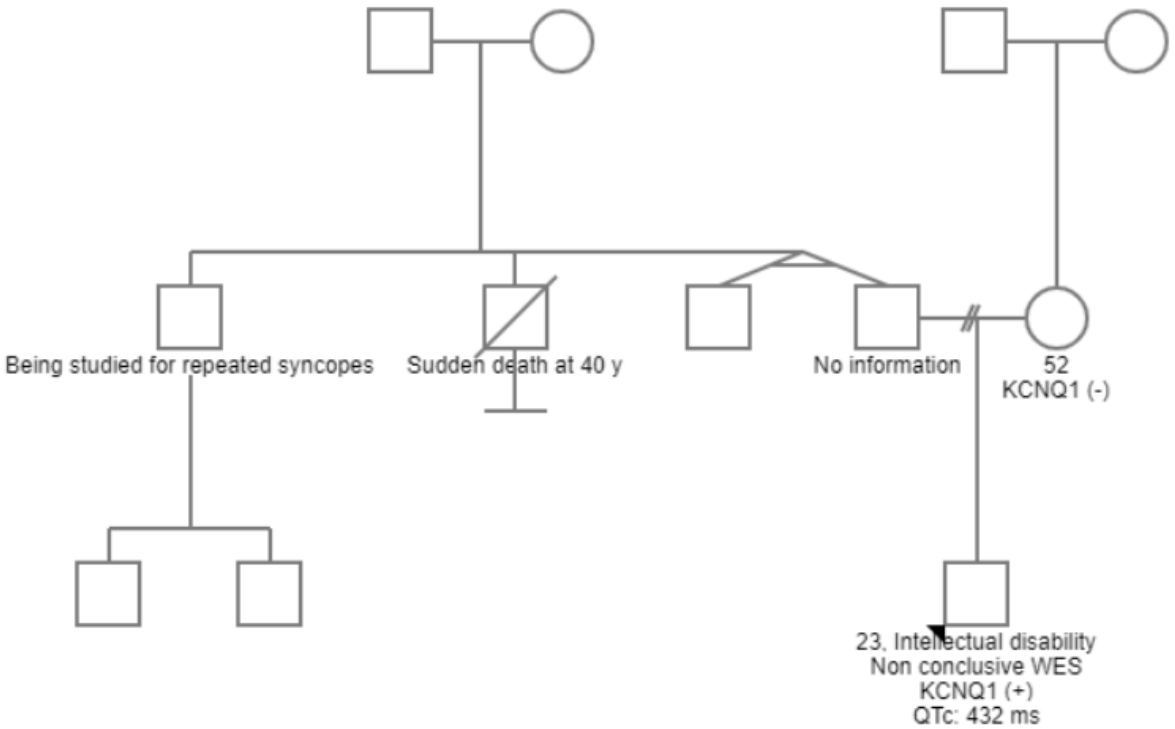
RESULTS: CLINICAL MANAGEMENT

Condition	Number of families	Number of carriers	Changes in clinical management
Hereditary paraganglioma	3	9	**Diagnosis of paraganglioma in 3 individuals at 35, 55 and 10 yo**
Hereditary breast cancer	4	8	Started follow-up
Hipertrophic cardiomyopathy	3	5	Started follow-up
Lynch syndrome	4	7	Started follow-up, **1 carrier with two low grade adenomas**
Long QT syndrome	5	10	Started follow-up, **4 carriers with long QT diagnosed at ECG; beta blocker treatment started in all carriers**
CPVT	1	1	Not available (cardiac transplantation due to primary condition)
Arrythmogenic cardiomyopathy	4	10	Started follow-up
Ehlers-Danlos	1	1	**Mild aortic dilation**
Familial hypercholesterolemia	2	4	1 carrier with **hypercholesterolemia** (previously known)

RESULTS: FAMILY WITH A SF IN SDHB (Familial paraganglioma)



RESULTS:RESULTS: FAMILY WITH A SF IN KCNQ1 (Long QT syndrome)



RESULTS: PSYCHOLOGICAL IMPACT

Clinical and psychological implications of secondary and incidental findings in cancer susceptibility genes after exome sequencing in patients with rare disorders

Estela Carrasco [1,2,3] Adrià López-Fernández [1,3] Marta Codina-Sola, [4,5,6] Irene Valenzuela, [4,5,6] AM Cueto-González, [4,5,6] Guillermo Villacampa, [7] Victor Navarro, [7] Sara Torres-Esquius, [3] Dolors Palau, [4,6] Mara Cruellas, [1,3] Maite Torres [1] Belen Perez-Dueñas, [8,9] Anna Abulí [4,5,6] Orland Diez, [3,4,6] Constantino Sábado-Álvarez, [10] Elena García-Arumí, [4,5,6,9,11] Eduardo F Tizzano [4,5,6] Lucas Moreno, [10,12] Judith Balmaña [1,3,13]

- Same Spanish cohort.
- Focused on carriers of cancer-related SF
- 11 index cases, 53 carrier relatives.
- Comparison of MICRA scores between carriers of SF vs probands with positive results with personal or familial positive history.
- Total MICRA scores and **subscales statistically significant higher**, but **overall low** and not significant clinically.

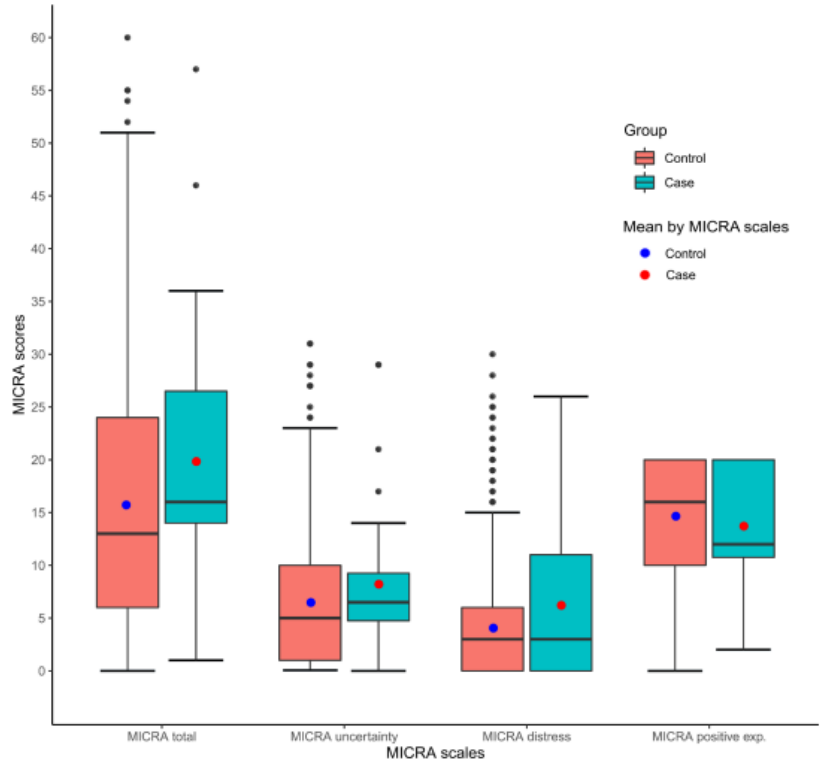


Figure 3 Distribution of MICRA scale and subscale scores between cases (n=32) and controls (n=576): total MICRA score (range 0–105), uncertainty (range 0–45), distress (range 0–30) and positive experiences (range 0–20). MICRA, Multidimensional Impact of Cancer Risk Assessment.

RESULTS: SUMMARY

- High acceptance rate (90%)
- Prevalence of 3,6%
- Disclosure has allowed early detection, prevention or clinical follow-up in some cases
- Need to manage in the context of an MTD team:
  - Extensive pre-test and post-test genetic counselling
  - Variant and case interpretation (innocent until proven guilty)
  - Follow-up and management
- Still debating a lot of points:
  - *Informed consent*
  - Penetrance
  - Increasing list: still reviewing and debating 3.1 version

Vall d'Hebron Hospital

Vall d'Hebron Institut de Recerca

VHIO VALL D'HEBRON Institut d'Oncologia

Cemcat Centre d'Esclerosi Múltiple de Catalunya

UAB Universitat Autònoma de Barcelona

Vall d'Hebron Barcelona Hospital Campus

Management of unexpected findings in the NHS England Genomic Medicine Service

Speaker : Mrs Rachael Mein

From : NHS England Genomics Unit Senior Laboratory Advisor (Rare Disease),UK

Management of unexpected findings in the NHS Genomic Medicine Service

Speaker : Rachael Mein

From : Genomics Unit, NHS England

Principles

1. Primary referrals for genomic testing are **clinically appropriate** and guided by the NHS National Genomics Test Directory

2. The potential for unexpected findings is **discussed** with the patient and/or parents **prior to testing**

3. **Appropriate reporting** and **management** of unexpected findings

Appropriate analysis

- Pipelines developed to minimise detection of unexpected finding
  - Parent-child trio's used for "gene agnostic" exome/genome analysis or very large clinically broad panels where inherited variants are filtered out unless compatible with Autosomal Recessive inheritance
  - Analysis which considers incomplete penetrance is more challenging, therefore a more targeted gene panel/virtual gene panel approach is favourable
- Not necessary to search for evidence of pathogenicity and classify a variant when it is not annotated as pathogenic and where the gene is clearly not relevant to phenotype in proband
- Additional studies to confirm or refute pathogenicity of unexpected findings are not routinely undertaken, due to the high likelihood of raising unnecessary anxiety and risk of potentially exhaustive family studies

MDT Discussion

- Discuss with laboratory Medical lead prior to informing referring clinician.
- Careful consideration should be given to the need to include unexpected findings in the formal laboratory report given it may be viewed by the patient and/or their family.

  - What is the clinical utility of the finding?
  - Is the finding predictive of future conditions?
  - What is the penetrance of the variant?
  - Is there high confidence in accuracy of the finding?
  - What interventions (e.g. surveillance, lifestyle advice) might be offered?
  - What is the primary diagnosis and/or prognosis of the patient?

Types of unexpected findings

Laboratory results not consistent with biological parentage

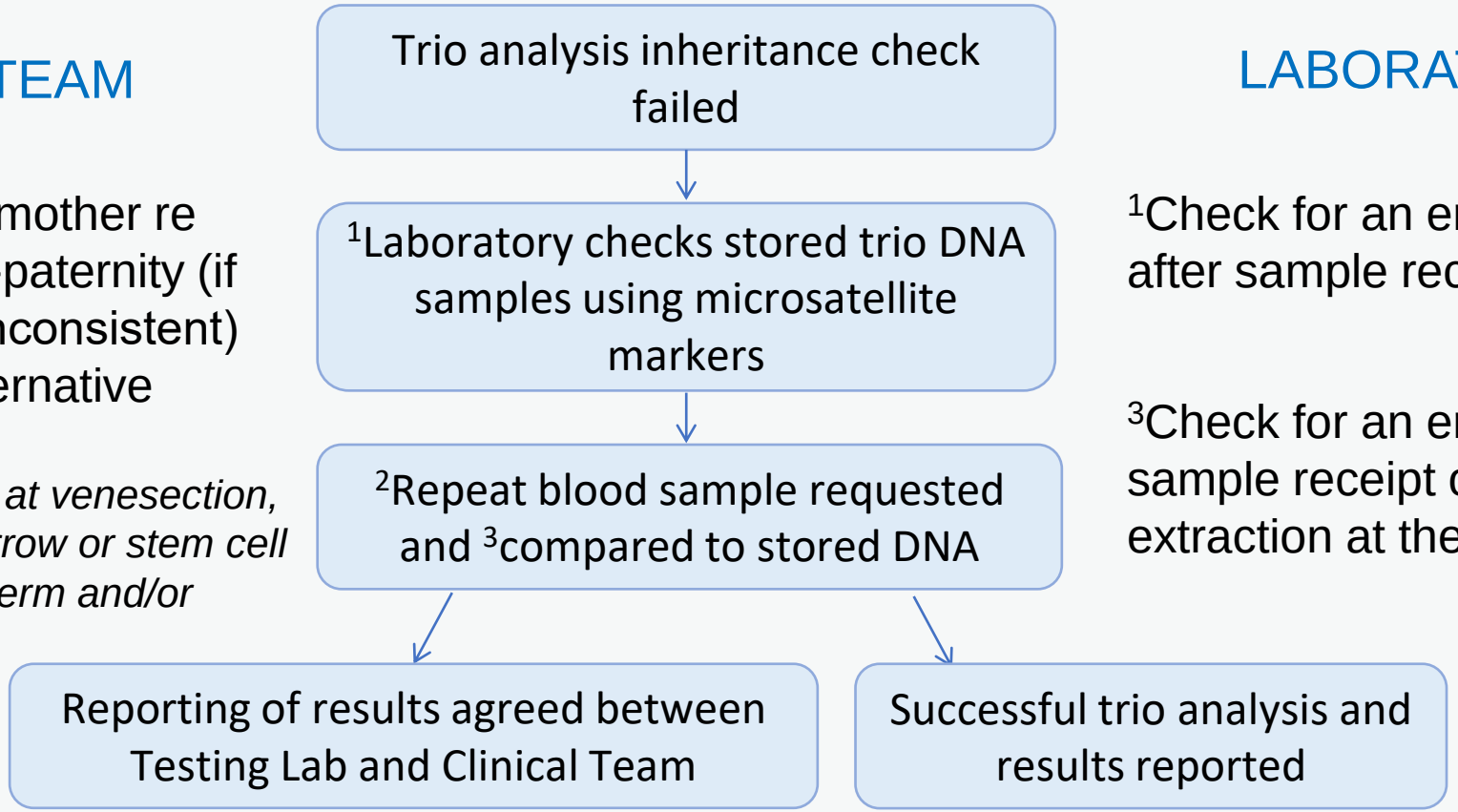
Clinically relevant variant(s) that are not related to the primary referral reason

Not actively sought
Clinically relevant to patient or family members

Results inconsistent with parental relationships

CLINICAL TEAM

[2]Discussion with mother re possibility of non-paternity (if father's sample inconsistent) and check for alternative explanation
(e.g. sample mix-up at venesection, allogeneic bone marrow or stem cell transplant, donor sperm and/or ovum)



LABORATORY

[1]Check for an error in testing lab after sample receipt

[3]Check for an error at venesection, sample receipt or during DNA extraction at the home GLH

National exome service for children with a likely single gene disorder

Unexpected variant finding in 34/4531 exome cases (0.75%)

G6PD deficiency in males
n=14
Drug-induced haemolytic anaemia

De novo pathogenic variants relevant to proband's future management
n=7
APC, SHOX, FBN1, CHD2, NIAA15, TGFB2, TRIM28

Autosomal recessive (biallelic) variants relevant to proband or siblings
n=7
FBXO7, PRKN, COG5, ALDOB, SLC22A5, GNRHR, SLC29A3

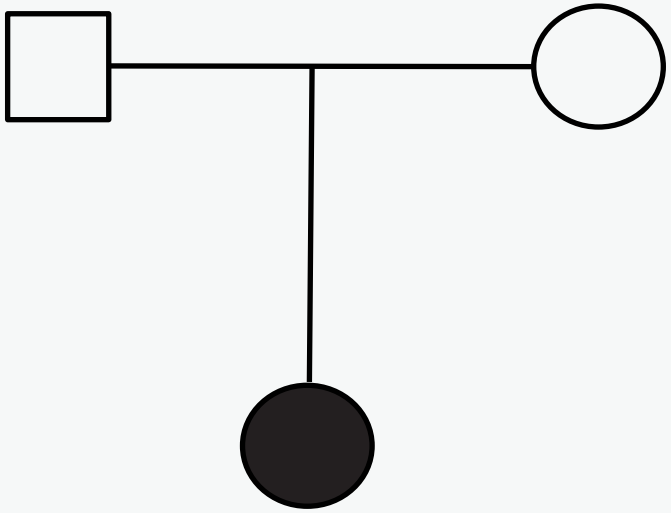
Inherited *BRCA2* variant
n=2

ABCA1 de novo and inherited variant (?AR)
n=1

De novo variant in fetus
n=2 *FLT4, FN1*

Paternal *DMD* exons 2-8 duplication
n=1

Is the variant related to the referral reason?



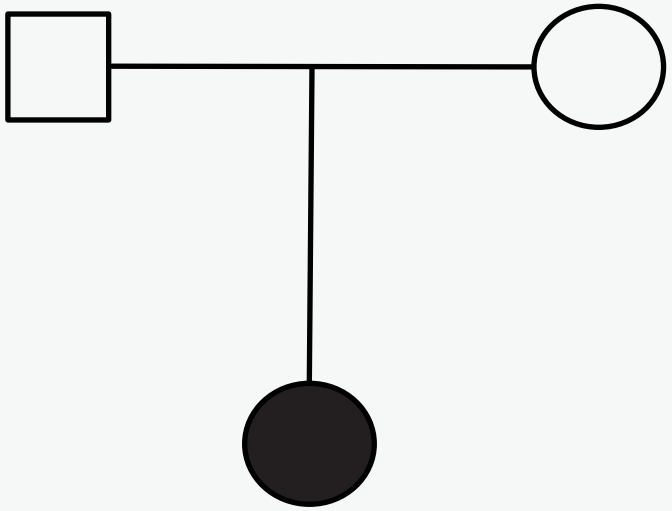
De novo PTPN11 pathogenic missense
De novo EXT2 nonsense

Presentation
5 month old baby with gastro-oesophageal reflux, cardiomyopathy, characteristic facial appearance, increased bone age.

PTPN11; Autosomal dominant Noonan syndrome
EXT2; Autosomal dominant multiple exostoses

Radiology review post-exome analysis
There are some enlarging rib lesions that were previously reported as likely healing rib fractures following a resuscitation. Reviewing the X-rays in light of the *EXT2* variant has confirmed the lesions as exostoses.

Is the variant clinically relevant to the patient?



FBXO7 Hom pathogenic frameshift variant

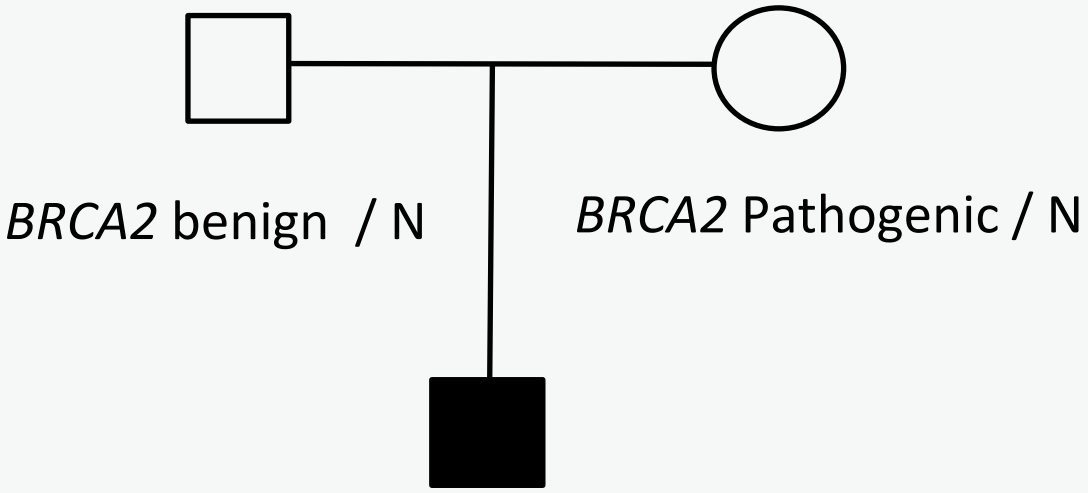
Presentation

Two year old with severe global developmental delay, hypotonia and renal failure

- Some reports of developmental delay in cases with biallelic *FBXO7* variants
- Does not explain full phenotype but uncertain if it is contributory
- May be clinically relevant for couple's other children

Very rare form of early-onset Parkinson disease: reported onset 10-19 years

Is it clinically relevant for a family member?



Presentation

2 week old baby in NICU

Tested via “gene-agnostic” trio (both parents and child) exome

Pathogenic *BRCA2* variant detected as prioritised due to biallelic segregation with benign variant

- Establish if known family history of breast/ovarian cancer
- Clinical Genetics input to discuss parental testing

Findings for which there are no evidence-based screening/treatment options

Leber Hereditary Optic Neuropathy
mitochondrial variants: m.3460G>A, 11778G>A and 14484T>C

Patient with a **clinical presentation incompatible with LHON** tested for a gene panel that includes these variants (e.g. Inborn errors of metabolism)

These pathogenic variants are not reported in this situation because:

(i) carrier frequency in the general population is high
(ii) the penetrance is low (50% of males and 85% of females do not develop blindness)
(iii) the lack of any proven available effective therapeutic intervention
(iv) the high likelihood of raising unnecessary anxiety for the patient and through potentially extensive family studies

Low penetrance, limited actionability

40 year old female with Ataxia
SDHA variant prioritised by “Exomiser”

Gene/variant not relevant to patient’s clinical presentation

SDHA variants display very low penetrance and there is no current consensus on whether screening should be offered
Not Reported

Child with syndromic intellectual disability
Comp. Het. for *SERPINA1* S and Z alleles (Alpha-1-antitrypsin) prioritised by Exomiser

Gene/variant not relevant to patent’s clinical presentation

Slightly elevated risk of lung disease in smokers but penetrance of SZ genotype is low, no change to clinical management and cascade testing is not indicated
Not Reported
(ZZ genotype is reportable as penetrance much higher)

Benefit of reporting the finding is greater than harm

Male neonate with congenital abnormalities
Hemizygous pathogenic *G6PD* variant inherited from unaffected mother

Variant not relevant to patient's clinical presentation and has no clinical phenotype in absence of environmental trigger

Report variant
to enable limitation of triggers that induce haemolytic anaemia

Summary

- Is the genetic finding/variant(s) relevant to the reason for referral for the genomic test?
- If not recommend to only report unexpected finding if;
  - High confidence in **accuracy** of finding and,
  - Predicted to be **Pathogenic** according to ACMG/ACGS variant interpretation guidance, and
  - **Penetrance** of variant(s) is high, and
  - There is **actionability,** and
  - The **benefit**, of returning the finding **outweighs** the potential **harm**, to the patient and/or family
- However, decision to return unexpected finding to the patient/family is the responsibility of the referring clinician following multi-disciplinary team discussion

Studies for exploring the expectations of patients/families regarding additional findings from exome sequencing in France

Speaker : Laurence Faivre
From : CHU Dijon-Bourgogne, Dijon, France

Studies for exploring the expectations of patients/families regarding additional findings from exome sequencing in France

Laurence Faivre, MD-PhD
November 28, 2023

ITHACA Webinar

INTRODUCTION

➢ In France, French laws permit :

✓ Return of results from IF, including in prenatal settings

✗ No proposal to access SF

? Benefit-risk ratio?

✓ **Research studies are encouraged in real-life situations**

Two French studies on secondary findings (SF)

FIND: Secondary findings produced by ES in a diagnostic context: from patient needs to organizational modalities

- Inclusions: 2017-2019
- Analysis and reporting: 2018-2021
- End of follow-up: 2019-2022

DEFIDIAG-DS: unexplored questions from FIND (GS)

- Inclusions : 2021-2023
- Analysis : 2022-2023
- End of follow-up: 2022-2024

FIND STUDY: Objectives

- **Objective:** Evaluate and analyze the medical, psychological, ethical and medico-economic impact of the active search for actionable SF out of ES data prescribed in a diagnostic context (developmental disorders).
- **Multidisciplinary team** of FHU-TRANSLAD: clinical and molecular geneticists, genetic counsellors, psychologists, health economists, ethicists, sociologists, anthropologists, methodologists, representants of patients support groups
- **Three national centers** of expertise for developmental anomalies (Dijon, Lyon, Paris-Pitié)

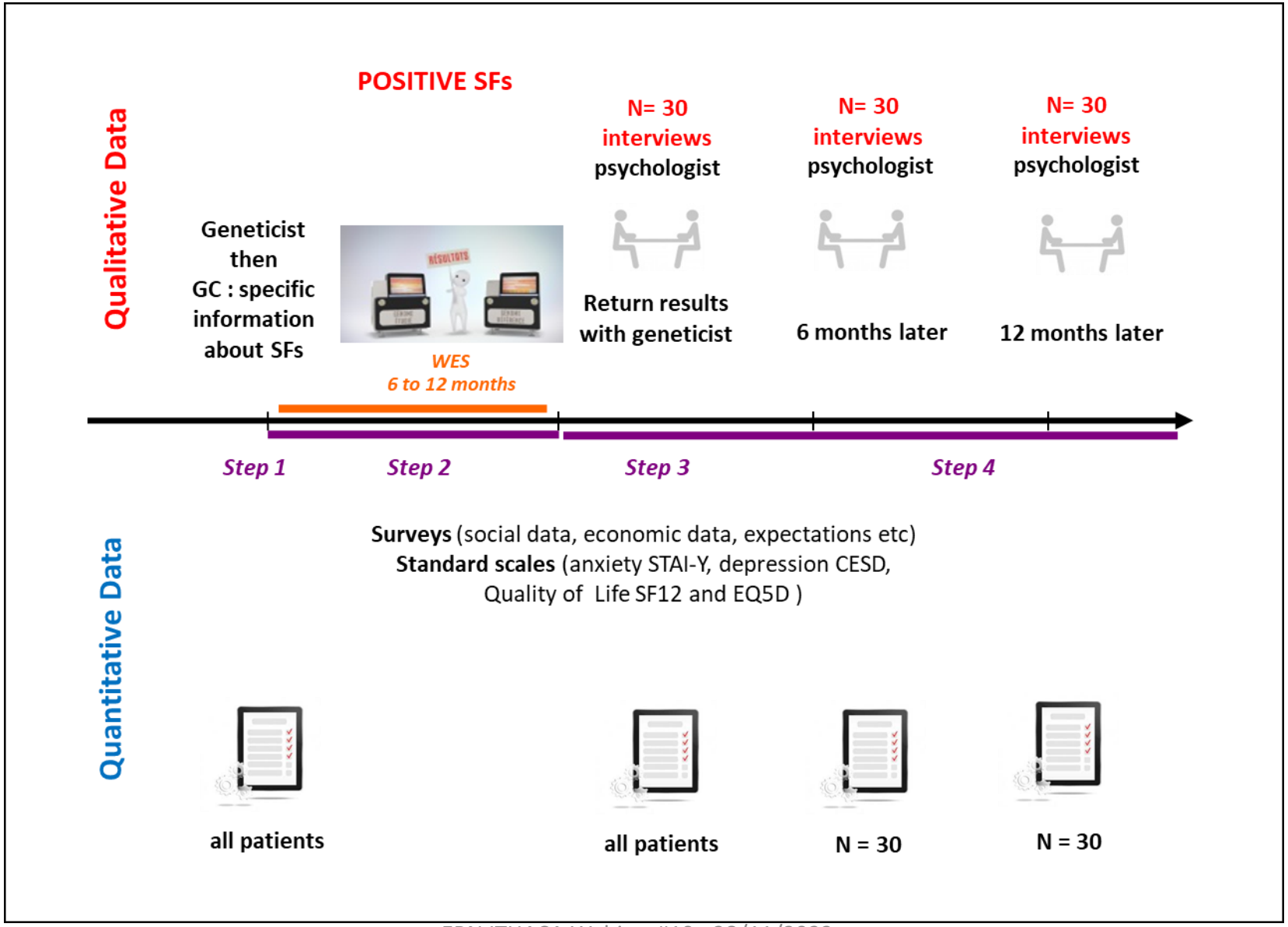
ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

SF1: ACMG+, mainly genetic predisposition to cancer, cardiac or metabolic diseases

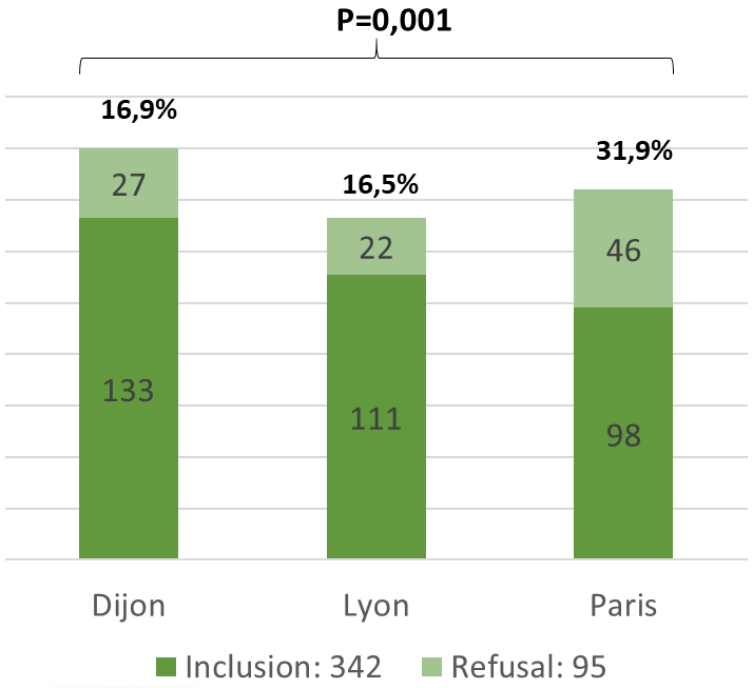
SF2: heterozygous carriers of recessive or X-linked diseases for procreation purposes

SF3: Pharmacogenomics

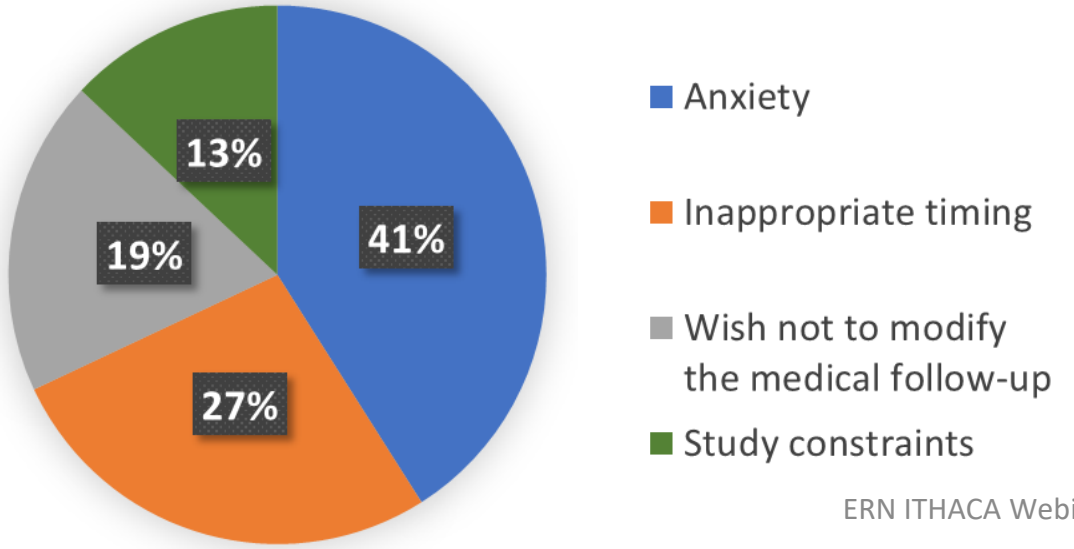
FIND DESIGN: Mixed methodology and longitudinal study

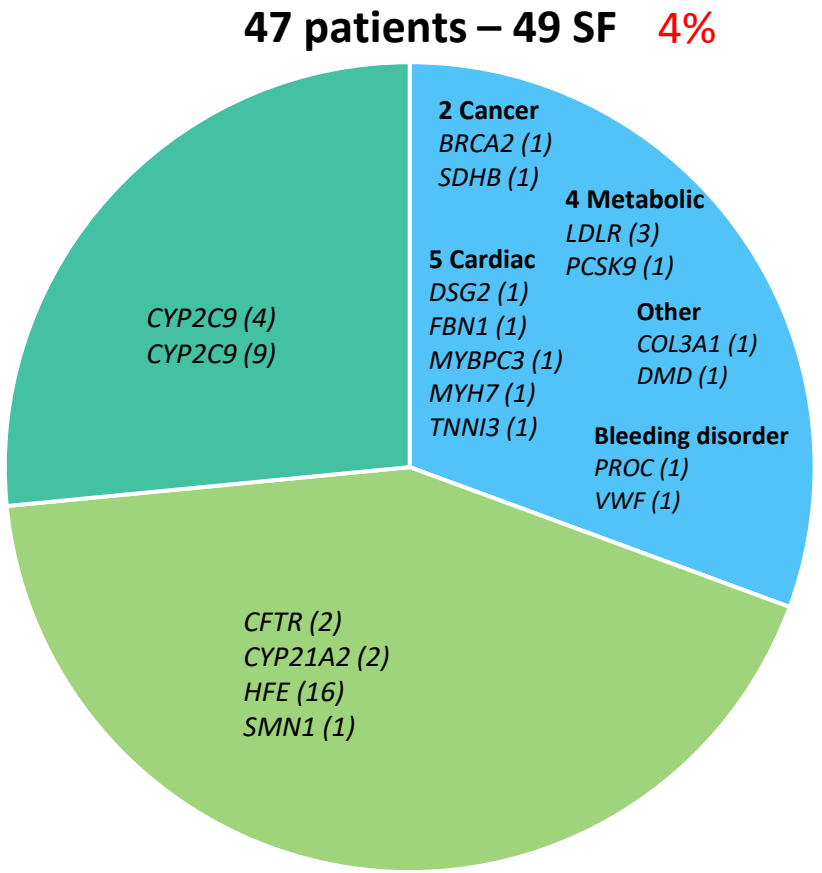


RESULTS : Opting out and repartition of SF



342 participants, 54% male, 46% female
73% with intellectual disability
Median age: 10 years (fetus – 68 years)





FIND RESULTS: Hypothesis and results

Hypothesis 1: Existence of a significant demand for access to SF in the French population	**CONFIRMED** **80% acceptance,** but with significant variation between centers suggesting the **influence of medical discourse** in this choice
Hypothesis 2: Problem of understanding the objectives of the SF research and the reporting of results	**CONFIRMED**
Hypothesis 3: Psychological impact on parents of the announcement of a SF + (> in case of late onset diseases)	**PARTIALLY CONFIRMED** Parents' initial psychological state (depression, anxiety) = predictive index of strong psychological reactions to results. Higher for group 1, decreases over time
Hypothesis 4: Risk of regretting accessing this research after understanding its personal and family implications	**NOT CONFIRMED**

FIND RESULTS: Hypothesis and results

Hypothesis 3

Little change *in anxiety and depression scores on standardized scales*

But non-zero psychological impact in group 1 and influence of personal psychological and situational history

Hypothesis 4

No REGRETS
High level of satisfaction (>90%)

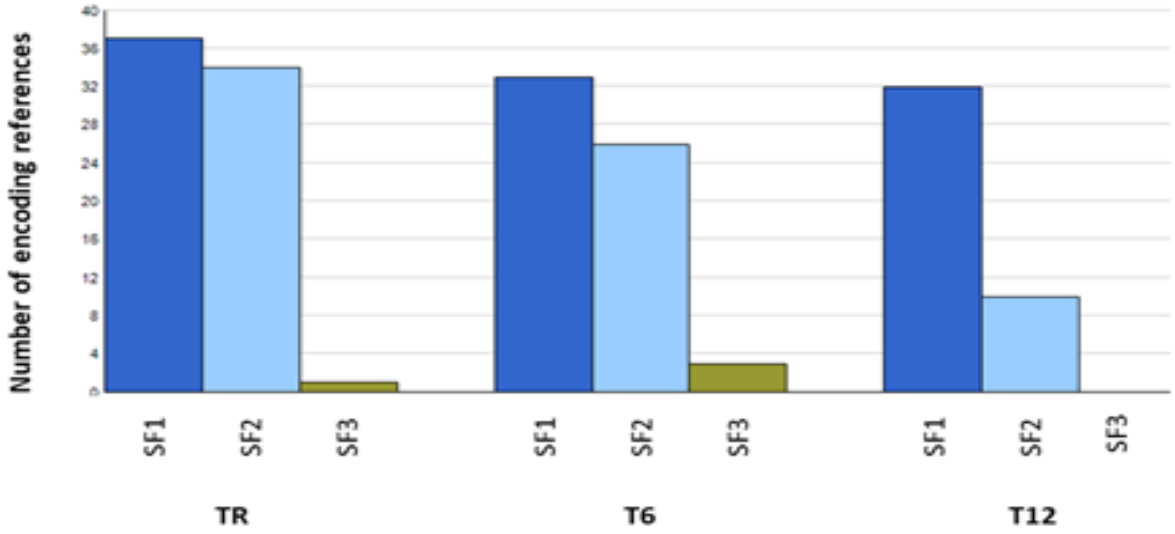
Reasons for satisfaction

Adaptation of care Information for the family

Group 2: knowledge of risk of transmission

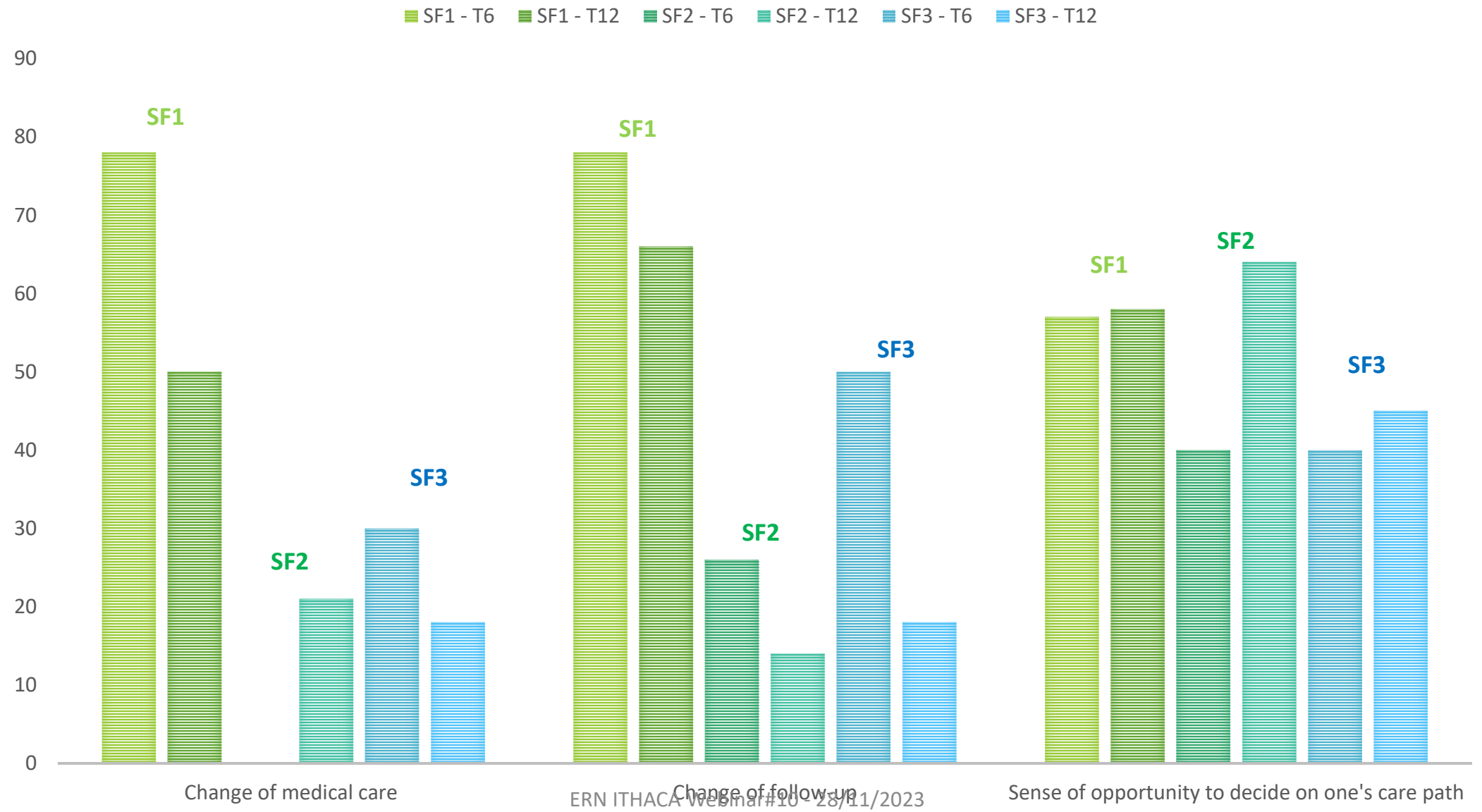
Group 3: information for doctor and avoidance of complications

ACTIONABILITY



Evolution of worry and anxiety in the interviews as a function of the type of SF and time

FIND RESULTS: Actionability?



FIND: Discussion

- **The primary diagnosis remains the main clinical demand.**
- Not all participants remembered the information given on the SF even with a dedicated information.
- **Decision-making in a context of parental responsibility** for a child with an undiagnosed rare disease. *"From the moment we know we have this possibility of knowing, we can no longer say no. We are obliged by duty for our children to do it."*
- **Information overload** at the time of the information and at time of the result, especially when there is a positive diagnosis and a SF, or even 2.
- The question of immediate actionability is not obvious in all cases.
- But unexplored data that justified DEFIDIAG-DS:
  - The question of minors, the demand will be the same when targeted at parents?
  - Further exploring the influence of medical discourse on decision-making and situations where people choose not to access SF, the impact of less information, the results reporting choices
  - Increasing the number of people screened with SF+ group 1

Recommandations from FIND

- Taking an interest in the patient's attitude regarding uncertainty and their history of depression and anxiety
- Offer separate consultations for PD and SF reporting
- Plan a consultation with a psychologist for the most anxiety-provoking announcements
- Anticipating medical follow-up and networking with specialists

DEFIDIAG-DS STUDY: Mixed and longitudinal design

DEFIDIAG-DS

When?

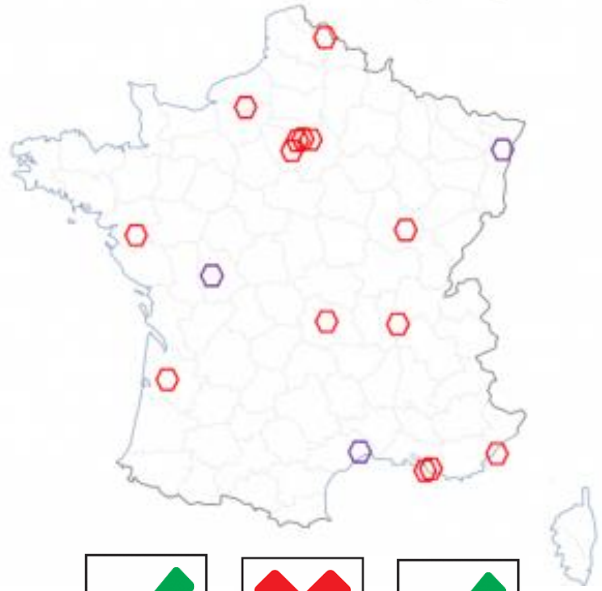
At time of results of GS

To whom?

Parents who changed their mind	Parents refusing access to SF	Parents with positive SF

What?

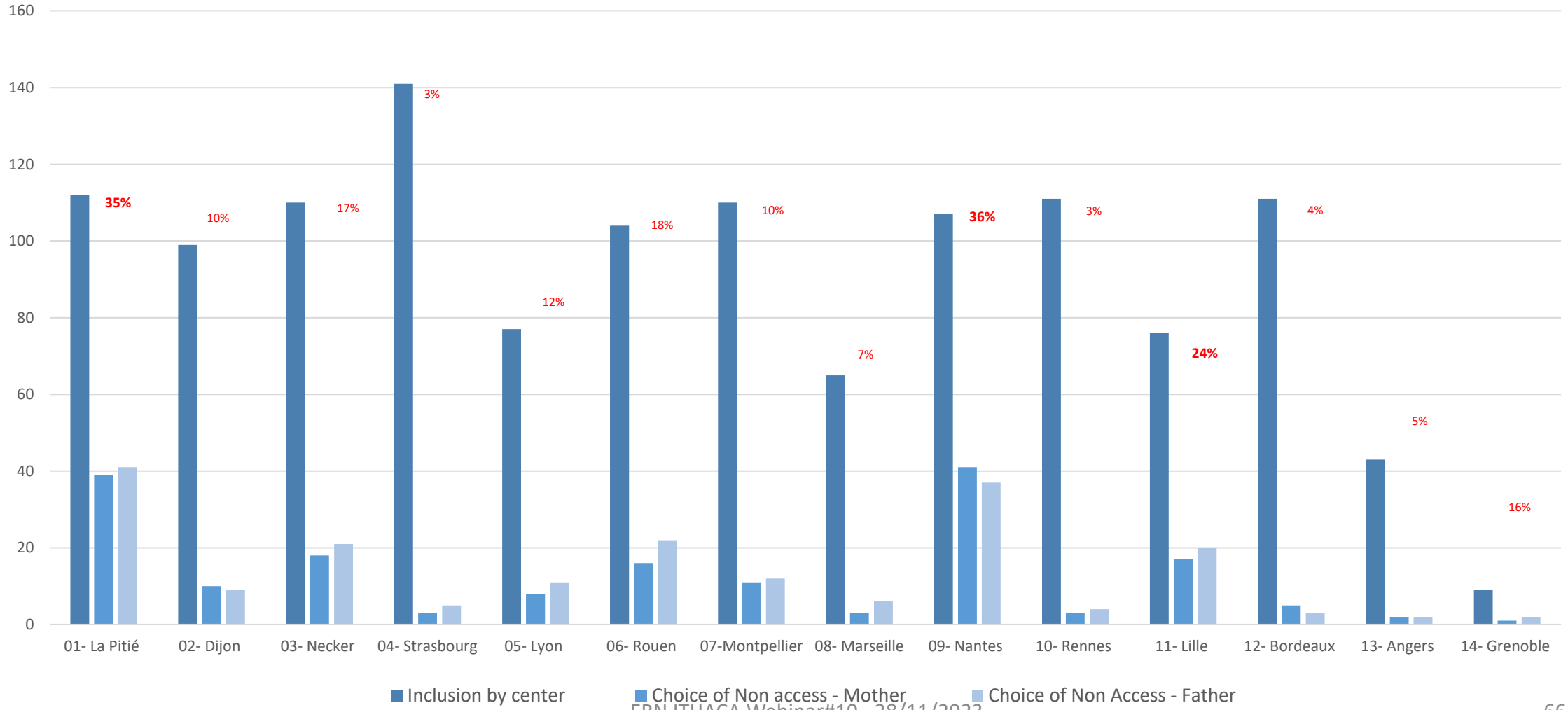
Parents who changed their mind	Parents refusing access to SF	Parents with positive SF
1 questionnaire	1 questionnaire 1 semi-directive interview	**At time of results:** 1 questionnaire 1 semi-directive interview **At 1 year after results:** 1 questionnaire 1 semi-directive interview



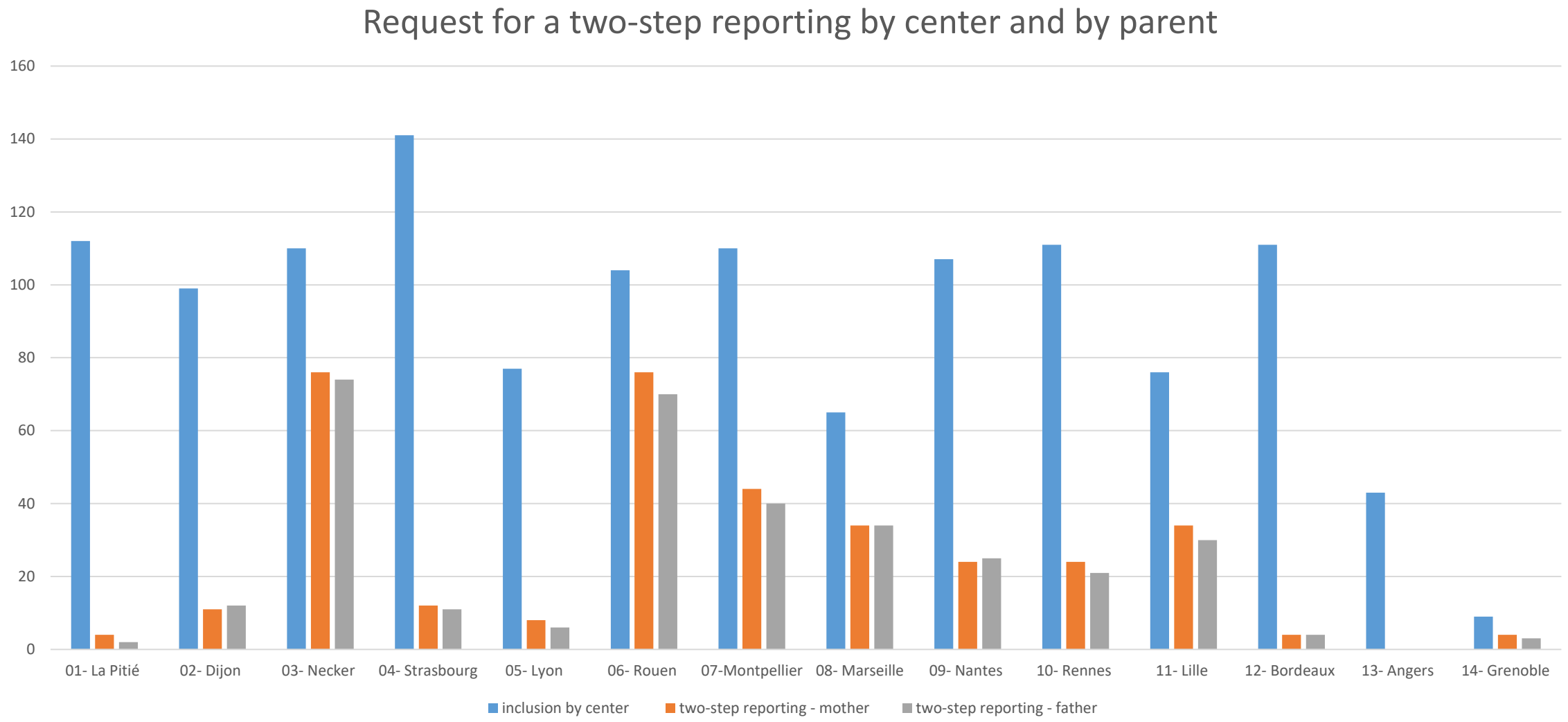
2400 parents, ACMG list only

DEFIDIAG-DS : Choice of opting out

Mothers : 177/1275 = 14%
Fathers: 195/1275 = 15%

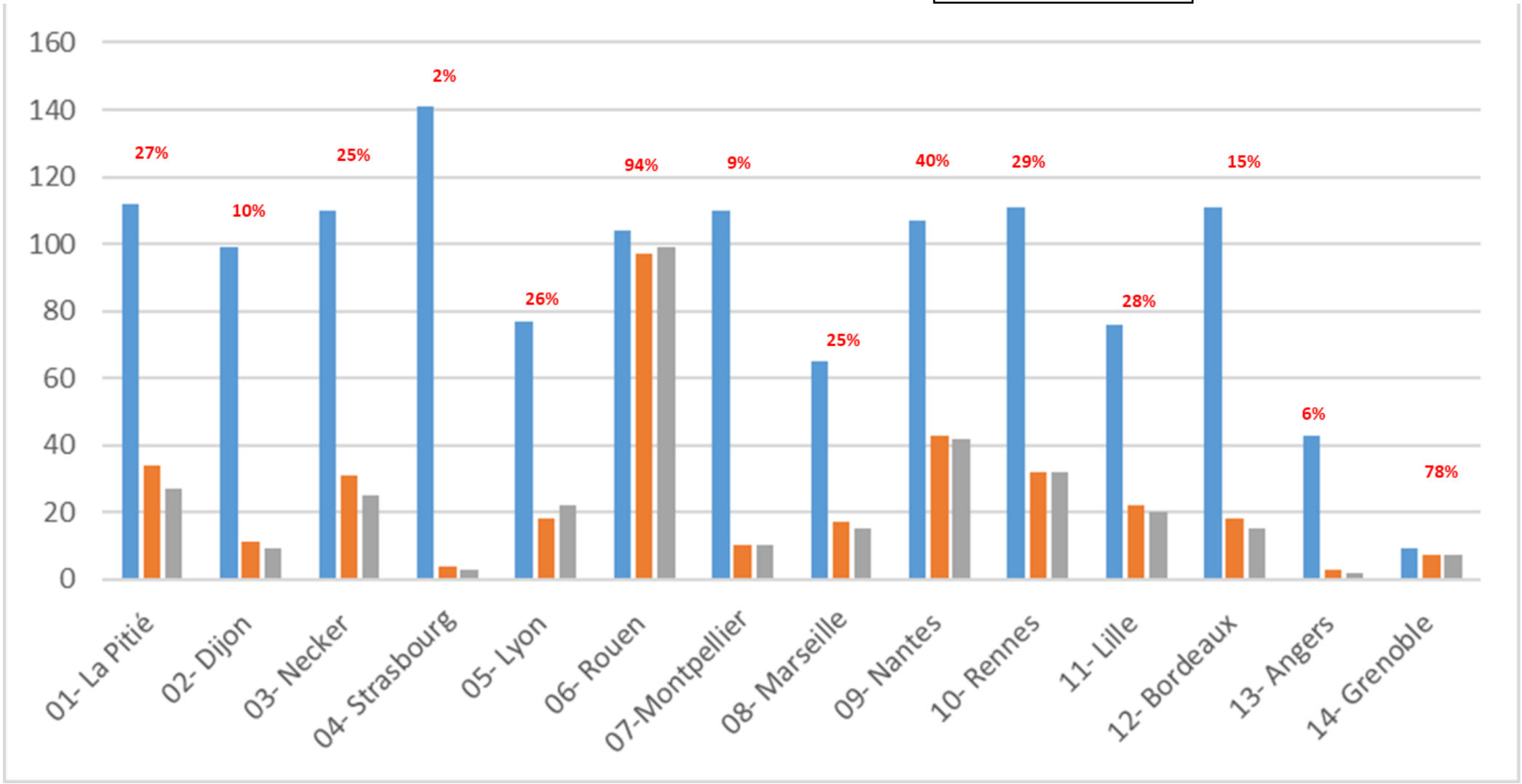


DEFIDIAG-DS : Choice for feed-back of results



DEFIDIAG-DS : Period of reflection

Mean 28 %



DEFIDIAG-DS : Preliminary psychological results

	Proportion	Raisons
Satisfaction (relatively to totally)	90% **100 % fathers**	Because of medical actionability 15/22 Because of the possibility to transmit results to family 15/22
Concerns (relatively to totally)	10/22 (45%)	Future risks generated by the announcement 8/10 Need for monitoring 7/10
No regret	**100%**	

Feelings generated by the announcement of these SF results

- The feeling of having had access to important information thanks to technological advances 15/22
- A little anxiety 5/22
- No feelings at all 1/22
- A thunderclap 1/22

Experience conditioned by the type of SF :

11/20 of parents who are not predisposed to cancer say that they have not been told they have a serious illness such as cancer or neurodegenerative disease.

PRELIMINARY DISCUSSION FROM DEFIDIAG-DS

- Analysis of differences when the proposal concern the parents himself and not the child: **not obvious and feasible**, but will depend on the law in each country
- Increasing of 12 centers to further analyse the influence of medical discourse on the choice of accessing to SF results, and results choice reporting: **confirmed…**
- Impact of less information on the comprehension: **not obvious**
- Increasing the number of people screened with ACMG SF+ : more experience on the impact of results and actionability **to be followed-up**

FOCUS GROUP FROM PROFESSIONALS

Concerns for themselves

- Professional paradigm shift
- Lack of knowledge/skills
- Difficult interpretation
- Weight of previous experience
- Lack of time and human ressources

Concerns for patients

- Clinical uncertainty
- Actionability sometimes questionable
- Risk of telescoping SF results
- Already vulnerable population, issue of minors
- Free and informed consent?

GENERAL CONCLUSION

- The question of SF allows greater anticipation than in the case of IF (information and list of genes), but remains prohibited by the new bioethics law in France
- The conclusions concerning psychological risks could be partly transposed to the question of IF
- Analysis of clinical actionability/usefulness remains an issue
- The question of access to minors remained to be defined in France by the implementing decree
- Questioning the scope of the genetic information sought, in a society that promotes risk control
- Results to be discussed with further research studies in real settings

Acknowledgements

- FIND researchers
- DEFIDIAG-DS researchers
- Inserm CIC 1432 - CHU Dijon Bourgogne- Module Épidémiologie Clinique
- Patients and their families

Main contacts: laurence.faivre@chu-dijon.fr, eleonore.viora-dupont@chu-dijon.fr, francoise.robert@chu-lyon.fr, christine.binquet@u-bourgogne.fr

Questions you want to ask

1. How many EU countries have a framework to allow diagnostic labs avoid the purposeful search for a secondary finding
2. Incidental findings (BRCA1/2) in minors
3. Could you please offer some clear guidance on if a VoUS should be reported, and if so, what criteria should the VoUS meet?
4. Incidental and secondary findings with regard to genome sequencing in pediatrics-what about later-onset conditions in children
5. How we harmonise nomenclature on secondary findings?
6. Do you think that countries who are driving forward active searches for secondary findings within genetic code are falling prey to confusion between diagnosis and screening? What are the panel's views on addressing this confusion (or perhaps conflation), thank you.
7. Will the group make a compilation of European legislation/national guidelines ? would be of great interest (the latest revision of Swiss Law added requirments for "résultats excédentaires"
8. Report of heterezogytes for AR diseases?
9. Risk is dependent on probability of occurrence and severity of consequence. Should the ease of mitigation also be a factor when determining the threshold for actionability and reporting of Incidental findings? eg if relative increased risk (severity x probability) is low-moderate but mitigation can be simple/behavioural should the finding be declared? (eg Factor V Leiden, alpha 1 antitrypsin)
10. For prenatal WES
11. has the discovery of incidental findings an immediate impact in the therapies adopted ?
12. What are the rules and how they are applied in other European countries for parents in a trio, for newborns and before birth?
13. anaging the incidental finding of cancer predisposition genes
14. Incidental findings (cancer predisposition) in minors, should it be reported or no?
15. Do you have individual policies for singleton and trio analysis on reporting of secondary or incidental findings?
16. In the various countries you observed : were the laws in agreement with the medical/ethical will ? (in particular for prenatal/people incapable of judgment analysis)
17. I will not be able to attend the webinar live, but hope to be able to watch it later via a webinar link by registering now?
18. Should the report of incidental findings include carrier states with reproductive impact?

Thank for answering our satisfaction survey

https://forms.office.com/e/EqmPfRUnvD

Thank you for your participation