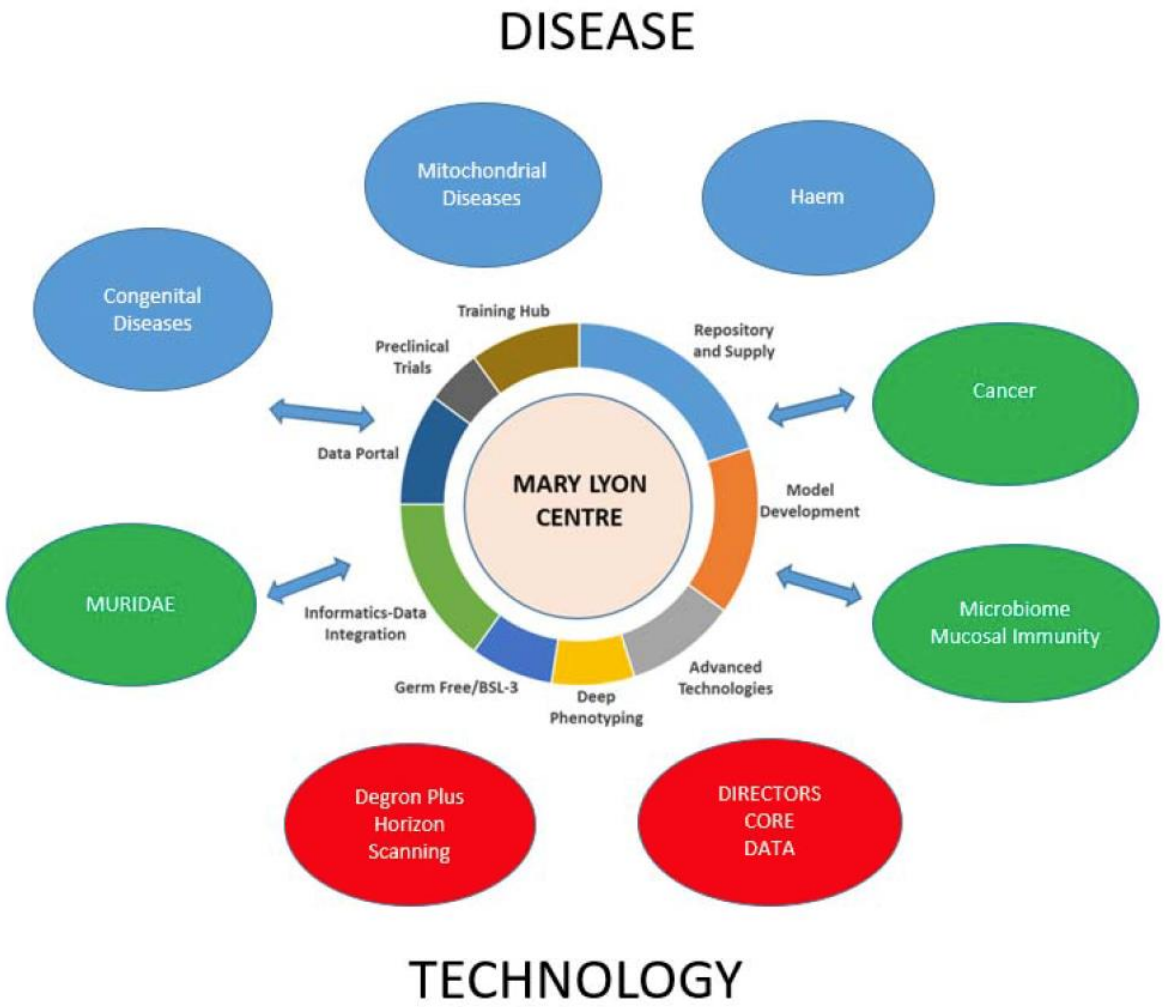
MRC National Mouse Genetics Network

Congenital Anomalies Cluster

The MRC National Mouse Genetics Network

https://nmgn.mrc.ukri.org/

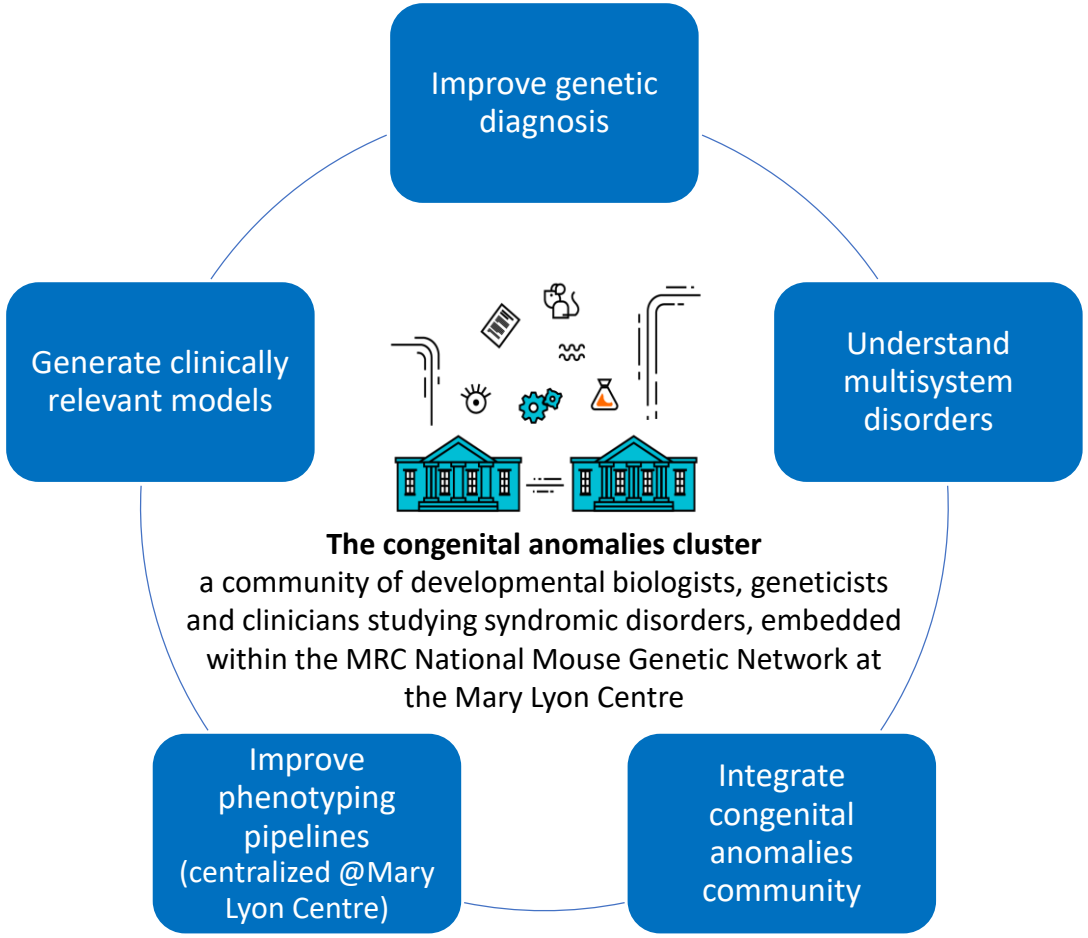


MRC National Mouse Genetics Network

Congenital Anomalies Cluster

Congenital Anomalies Cluster: Linking clinicians and model system experts

- Challenge: clinic ➡ genomics ➡ establish causality ➡ disease mechanisms



- Five developmental biology research teams

Nick Greene
ICH, UCL

Deb Henderson
Newcastle and HDBR

Karen Liu
CCRB, KCL

Pleasantine Mill
MRC HGU, Edinburgh

Steve Twigg
MRC WIMM Oxford

MRC National Mouse Genetics Network

Congenital Anomalies Cluster

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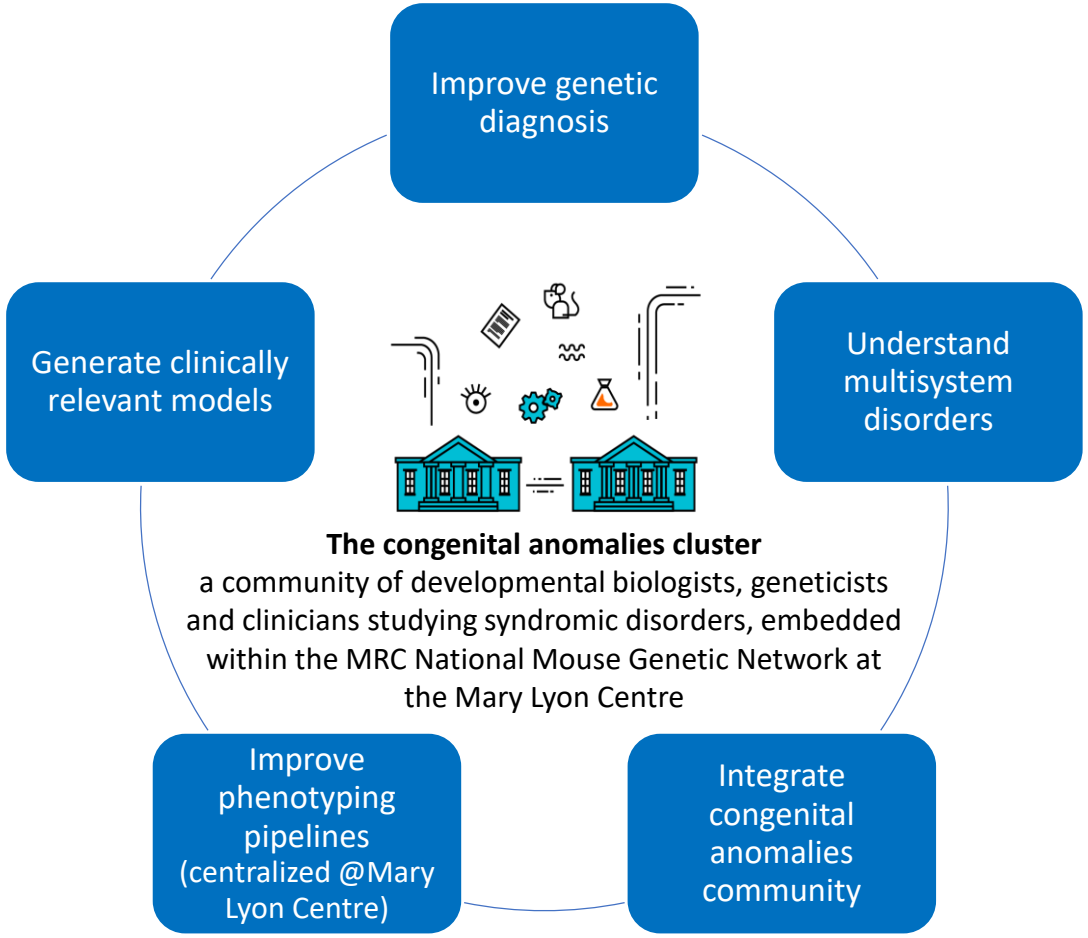
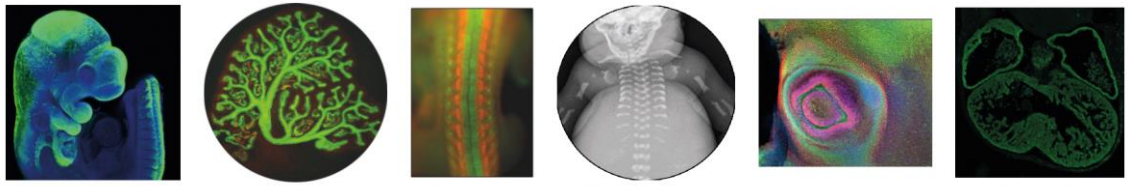


- Prioritise VUS in multisystem disorders where we have expertise

Systems and disease focus



MRC National Mouse Genetics Network

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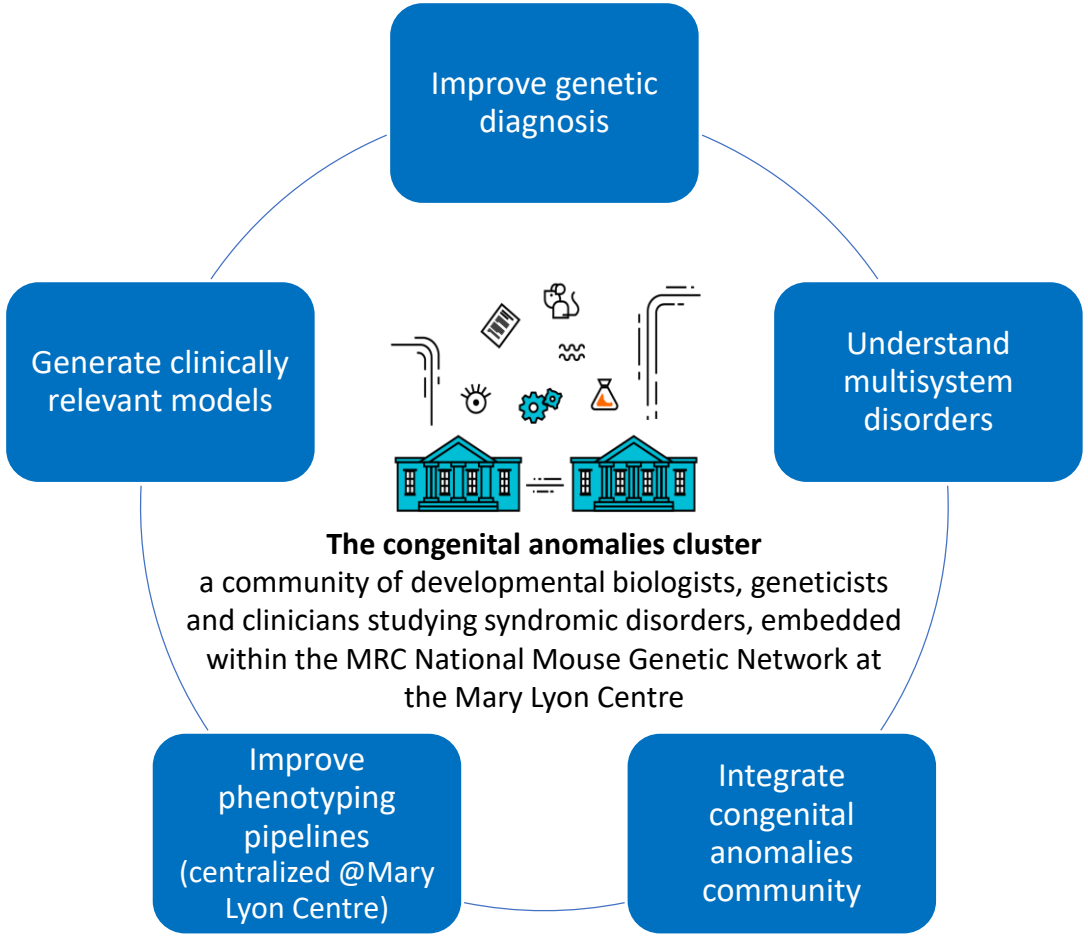
- Challenge: clinic ➡ genomics ➡ establish causality ➡ disease mechanisms



- Prioritise VUS in multisystem disorders where we have expertise

VUS of interest? Contact us:

https://nmgn.mrc.ukri.org/clusters/congenital-anomalies/

Stephen.Twigg@imm.ox.ac.uk

MRC National Mouse Genetics Network

Congenital Anomalies Cluster

Congenital Anomalies Cluster

2. Variant Screening Pipeline

Gene variants of unknown significance

Clinicians	Internal advisory board	Scientific community
Inputs from Genomics England, GECIPs, Decipher and pilot screens	Board to assess relevance, feasibility of allele generation and pipeline (F0 screening or line generation)	Identification of relevant human variants by the community

Variant submission portal

Assessment by the clinical advisory board

Variant selection by the internal advisory board

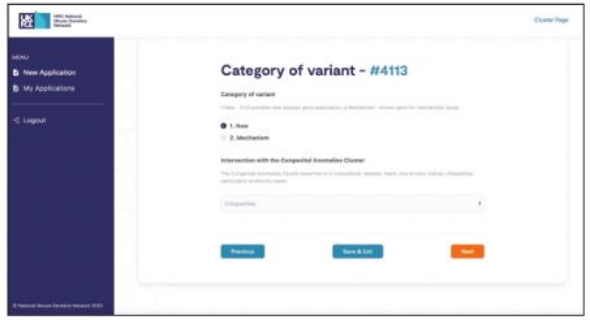
Candidate gene variants

F0 screening **Line generation**

3. Variant Submission Portal

1. Welcome to the Congenital Anomalies Cluster Genetic Database

   To start your submission please sign in or register for an account.

2. 

Information necessary for submission:

Entry details - *Category, Depositor, Intersection*

Clinical information - *Clinician, Consent, Features/diagnosis, HPO terms, Sex, Ethnicity, Relevant assessments/tests/assays, InheritanceV*

Gene information - *Gene, Known disease gene?, Chr, GRCh38, NCBI reference*

Variant(s) - *In GnomAD?, UK biobank?, CADD, REVEL, Gene pLi, cDNA, Protein, Exon, Domain, Mutational mechanism?*

Functional information - *Gene function, Functional analysis, Existing models?, IMPC*

Submitter comments and motivation - *Free space for additional information and motivation statement*

3. **Generation of a candidate variant information sheet for submission to the Clinical Advisory Board (CAB)**

4. **Candidate variant ranking by CAB**

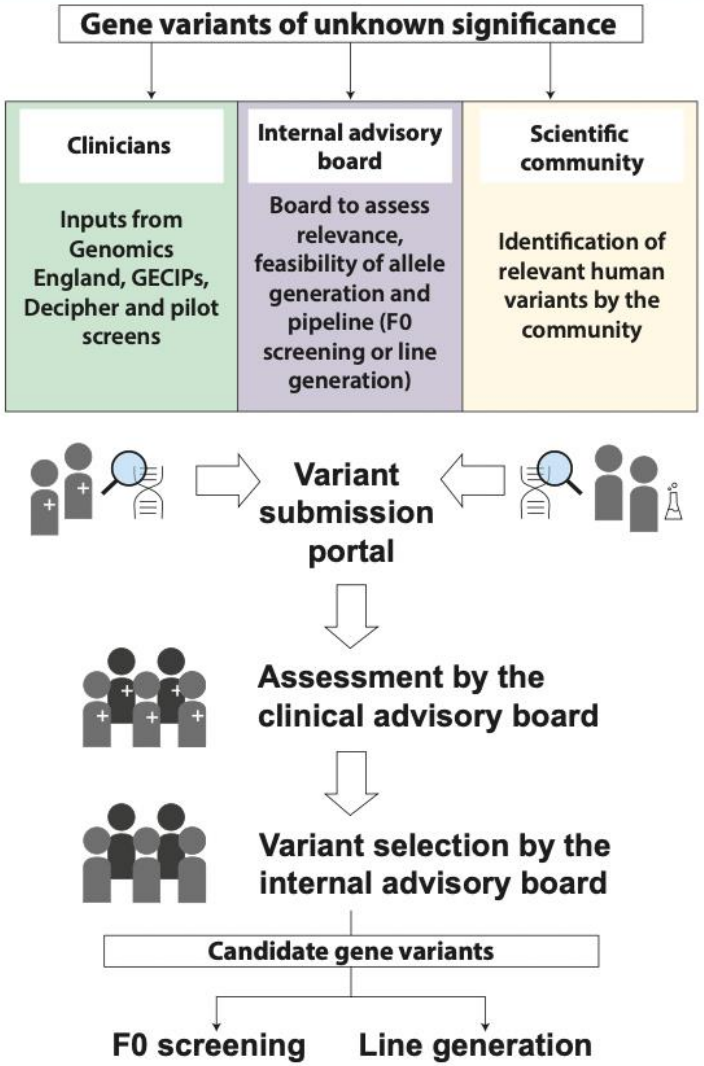
5. **Assessment of CAB scores and candidate variant selection by the Internal Advisory Board (IAB)**

MRC National Mouse Genetics Network

Congenital Anomalies Cluster

Congenital Anomalies Cluster

2. Variant Screening Pipeline



Clinical Advisory Board

Fowzan Alkuraya

Diana Baralle

Azeez Butali

Bernard Keavney

Damian Smedley

Stephen Robertson

Daniel Gale

Andrew Wilkie

Congenital Anomalies Cluster

MRC National Mouse Genetics Network

Congenital Anomalies Cluster

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F0 screening **Line generation**

Clinical Advisory Board

Contact
Steve Twigg/Andrew Wilkie (Clinician)
Research Consent - YES

Clinical Features
Father and daughter – with frontonasal lipoma, scalp defects, and congenital heart anomalies.
Father: born with cutis aplasia of scalp and a large facial lipoma, to unaffected nonconsanguineous parents. He required surgery in infancy for tetralogy of Fallot and a hypoplastic urethra.
Daughter: at birth prominent symmetrical mass extending from the forehead to the nasal bridge suggestive of a lipoma, and extensive cutis aplasia - posterior half of the scalp. PDA. Moderately-delayed expressive language skills, coordination difficulties and mild conductive hearing loss.

Gene: ***KCTD15***
VUS(s): p.(Asn104His)
Inheritance: *De novo*

Gene/variant metrics
pLI: **0.04**; gnomAD: **0**; CADD: **32**

Domain Information
Asn104 – BTB domain
The protein usually forms as a pentamer, with the BTB domain playing a key role in assembly.

Gene Function and disease:
KCTD15 Inhibits AP2 transcriptional activity by interaction with its activation domain; has a role in defining the neural crest region. There is no current link to Mendelian disease.

Functional analysis:
Biophysical analyses showed that the Asp104His substitution resulted in a monomeric BTB domain likely to be partially unfolded at physiological temperatures. A crystal structure of the BTB domain variant Gly88Asp revealed an abnormal closed *hexameric* assembly.

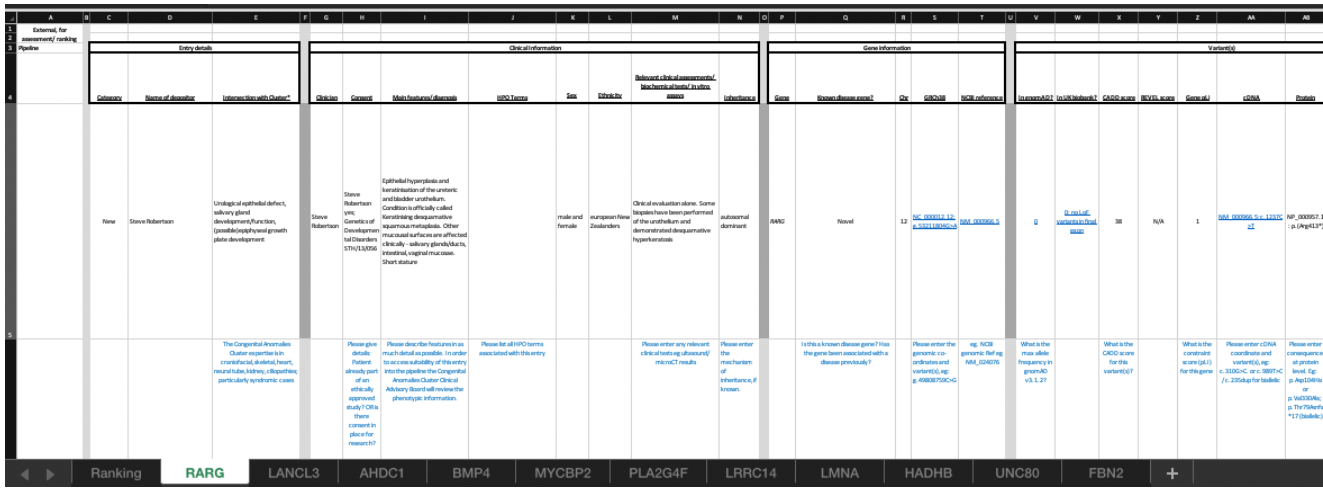
Functional analysis – mouse:
K/O: complete penetrance of preweaning lethality

RANK:

Supporting information
There is a second family with de novo *KCTD15* c.263G>A; p.Gly88Asp. Clinical features: sporadically affected proband presented at birth with a midline frontonasal mass. On review at the age of 15 years, she was noted to have thin, fair hair. KCTD15 Gly88Asp is in BTB domain and equivalent to KCTD1 Gly62Asp - previously reported to cause Scalp-ear-nipple (SEN) syndrome.

Submitter motivation:
Mouse generation would confirm pathogenicity and enable exploration of pathology. We have identified two families with frontonasal dysplasia (FND) that harbour de novo missense variants in the gene encoding potassium-channel tetramerisation domain-containing protein 15 (KCTD15). KCTD proteins form a large and understudied family defined by the presence of a BTB (Broad-complex, Tramtrack and Bric-a-brac) domain and have diverse functions including in DNA replication, transcriptional repression, protein degradation and hedgehog signalling. A disease association for KCTD15 has not previously been described, but heterozygous mutations in the highly homologous paralogue, KCTD1, cause scalp-ear-nipple (SEN) syndrome, characterised by cutis aplasia of the scalp and anomalies of the external ears, digits/nails, and breasts. It is therefore notable that both of our FND families have a phenotype that includes cutis aplasia of the scalp. Family 1 consists of a father and daughter with features including large fronto-nasal lipoma and cardiac defects (tetralogy of Fallot or patent ductus arteriosus) who both carry a heterozygous c.310G>C (p.Asp104His) variant. In Family 2 a de novo variant c.263G>A (p.Gly88Asp) is present in the proband who presented with a midline frontonasal mass and sparse hair. The occurrence of two de novo missense mutations, absent from databases of normal variation and affecting the same domain of the KCTD15 protein, in association with a clinically similar, extremely rare phenotype including frontonasal mass and cutis aplasia or sparse hair, is highly suggestive that these variants are causative of the phenotype. In collaboration with Prof Alex Bullock (Structural Genomics Consortium, Oxford) we demonstrated that the p.Asp104His substitution destabilises the pentameric assembly of both KCTD15 homodimers and KCTD15-KCTD1 heterodimers via this domain suggesting a dominant negative mode of action. Asp104 is conserved residue that makes key intermolecular contacts within the pentamer. Similarly, the Family 2 variant equivalent (p.Gly62Asp) has been identified in KCTD1/SEN syndrome and modelling suggests it may destabilise the protein structure and affect interaction with the neural crest transcription factor AP-22. Both KCTD1 and KCTD15 have been shown to repress AP2 and affect neural crest formation3-5. This is the first report of putative causative mutations in KCTD15, highlighting the critical role played by KCTD15 in tissues of neural crest and ectodermal origin.

VUS sheet



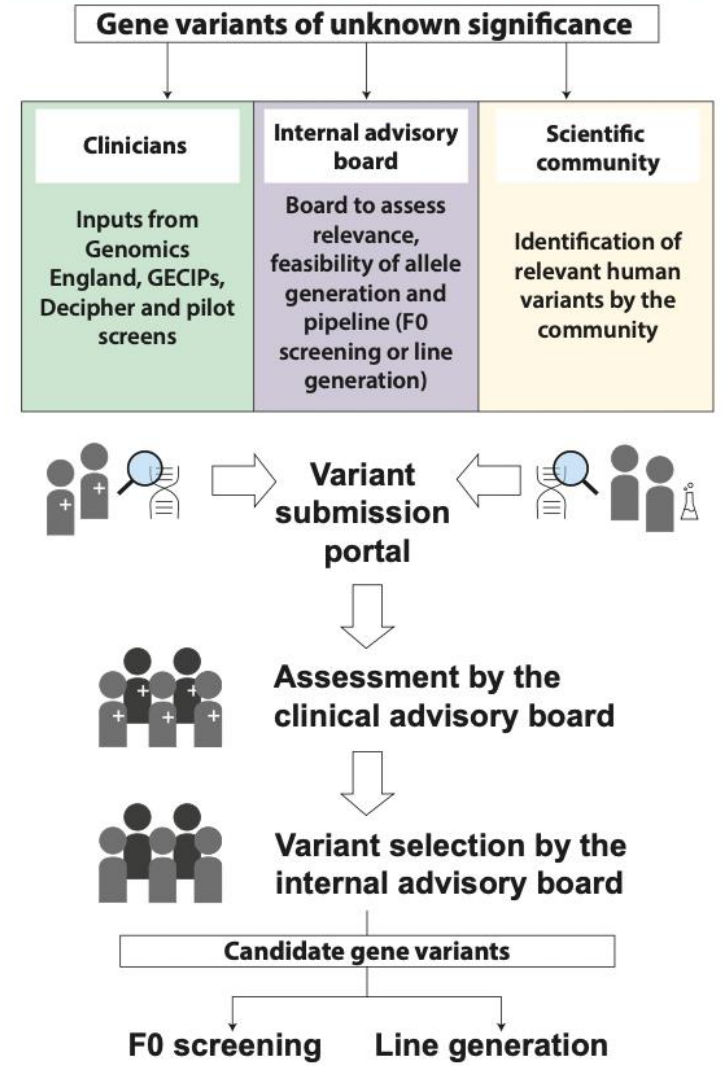
Full data spreadsheet

MRC National Mouse Genetics Network

Congenital Anomalies Cluster

Congenital Anomalies Cluster

2. Variant Screening Pipeline



Clinical Advisory Board

VUS ranking

Priorities (in order of importance):

- New disease gene
- Known disease gene, but new phenotype association or novel allelic disorder
- Known disease gene with difficult to interpret VUS, eg nearby SV, deep intronic SNV
- Known disease gene where deep phenotypic investigation of the mouse model could lead to new insights into pathogenic mechanisms

Considerations

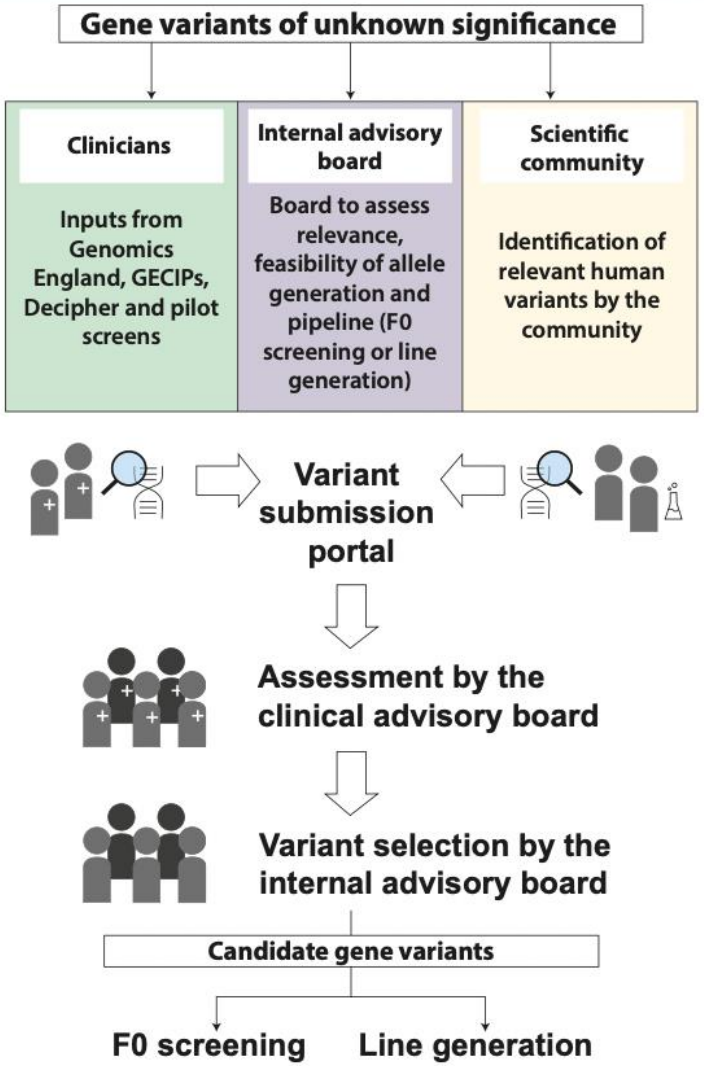
- The clinical features should overlap with the specialities of our developmental biology team: *craniofacial, skeletal, heart, neural tube, kidney, ciliopathies.*
- We are most interested in syndromic conditions to simultaneously study multiple systems in the mouse.

MRC National Mouse Genetics Network

Congenital Anomalies Cluster

Congenital Anomalies Cluster

2. Variant Screening Pipeline



Clinical Advisory Board

Gene	Variant	Allele	Inheritance	Depositor	CADD	REVEL	AlphaMissense	pLI	Score	Rank
	Arg413*	Het	AD, 3 gens		38	n/a	n/a	1	1.5	1
	Leu343Arg	Het	De novo		27.6	0.705	0.986 (path)	0	3.9	2
	c.370+441G>A	Het	De novo		19.28	n/a	n/a	0.96	4.3	3
	Gly2716Arg	Hom	AR		29.1	0.58	0.996 (path)	0.05	5.0	4
	Pro436Serfs*81	Het	De novo		n/a	n/a	n/a	1	5.1	5
	Asp2435Asn	Het	De novo		33	0.17	0.4735 (ambig)	1	5.56	6
	Phe130Cys	Het	De novo		24.2	0.572	0.4709 (ambig)	0	5.6	7
	Ala54Val	Het	De novo		15.65	0.03	0.1149 (benign)	0.04	5.76	8

MRC National Mouse Genetics Network

Understanding multisystem disorders

Congenital Anomalies Cluster

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Gene variants of unknown significance

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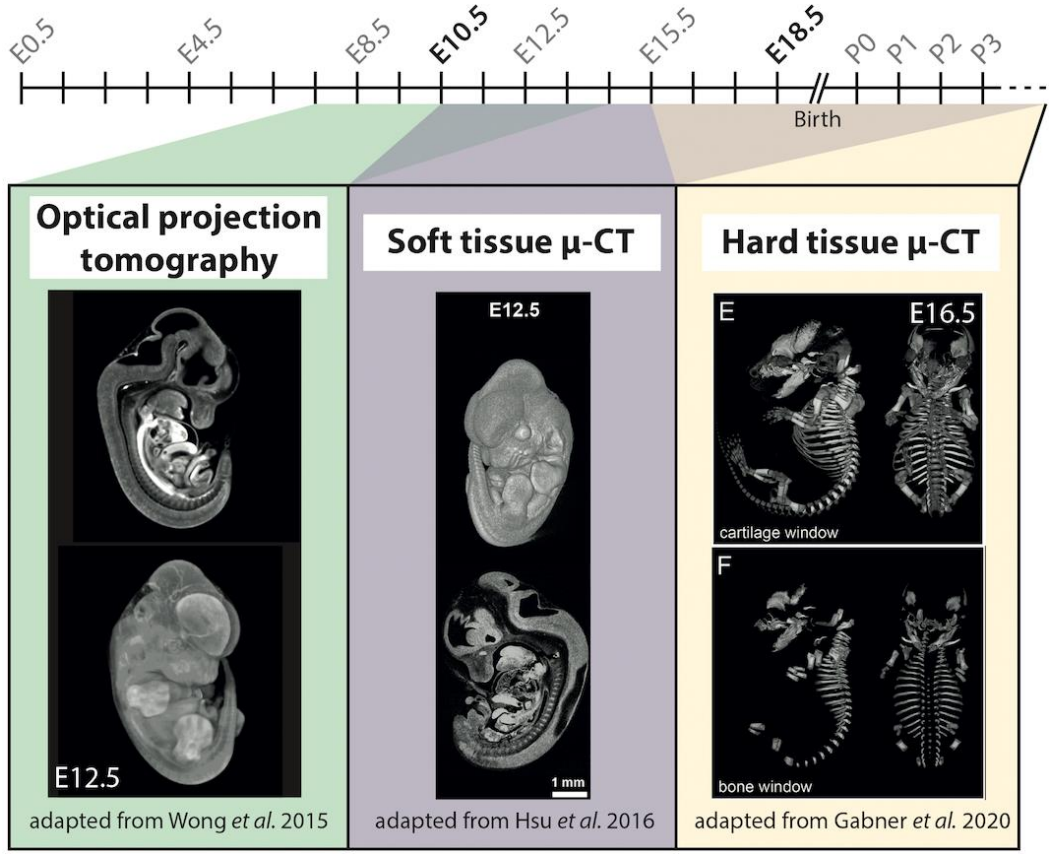
Candidate gene variants

F0 screening **Line generation**

Embryonic



Phenotyping

MRC National Mouse Genetics Network

Understanding multisystem disorders

Congenital Anomalies Cluster

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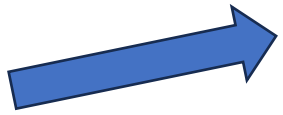
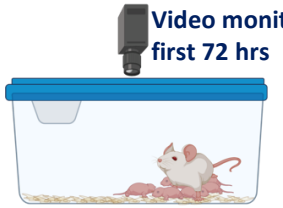
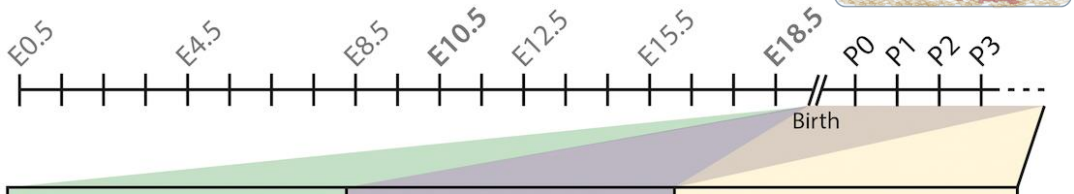




Perinatal



Maternal related behaviours	Pup related behaviours	Additional observations
- Time/position in the nest - Crouching and suckling - Pup retrieval - Grooming - Ultrasonic vocalisations - Feeding and drinking - General behaviour - Sleep behaviour	- Time/position in the nest - Suckling - Pup retrieval - Grooming - Ultrasonic vocalisations	- Presence of milk spot - Perinatal gasping - Pup colour - Brown adipose tissue changes

Phenotyping

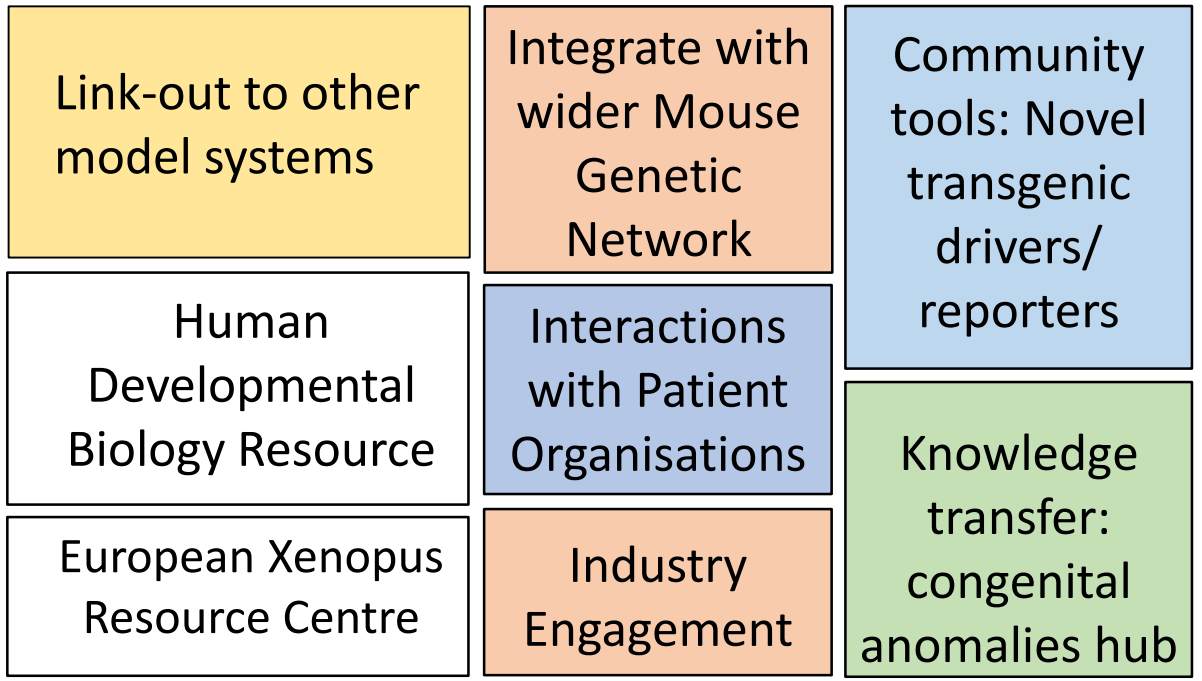
MRC National Mouse Genetics Network

Congenital Anomalies Cluster

Congenital Anomalies Cluster

Enhance UK expertise in determining causes, understanding mechanisms and identifying potential therapies for congenital anomalies

VUS of interest? Contact us:
https://nmgn.mrc.ukri.org/clusters/congenital-anomalies/
Stephen.Twigg@imm.ox.ac.uk



Community building

CRANIOSYNOSTOSIS WORKGROUP

European Reference Networks

ERN CRANIO annual meeting

November 17th, 2023

European Reference Network
for rare or low prevalence complex diseases
Network Craniofacial anomalies and ear, nose and throat disorders (ERN CRANIO)

Co-funded by the Health Programme of the European Union

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REGISTRY UPDATE

Two workstreams included:

Craniosynostosis

Cleft lip/palate

In progress:

Craniofacial microsomia

Congenital Deafness

Orodental

European Reference Network
for rare or low prevalence complex diseases
Network Craniofacial anomalies and ear, nose and throat disorders (ERN CRANIO)

MOLGENIS

CRANIOSYNOSTOSIS DATASET

Age in years

Craniofacial surgery (repeating*)

- Treatment information, transfusions, complications
- Reason for reoperation*

Preoperative visit

- Disease characteristics & general information
- Gestation and birth outcomes
- Head circumference and CI*
- Suture-specific photo score *
- Functional outcome (PE)
- ASQ

Follow-up visits

- Head circumference and CI*
- Suture-specific photo score *
- Functional outcomes
- ASQ
- SDQ
- Oxford PROM
- FACE-Q for children (head shape and forehead)

* if applicable

SCHEDULE

- Currently finalizing Molgenis system update:
  - Improved user-friendliness of registry
  - Creation of center and disease specific dashboards

- Workshops with will be organized focused on:
  - Data entry (bulk & manual)
  - SPIDER tool

- Aim: data entry from January 2024 onwards

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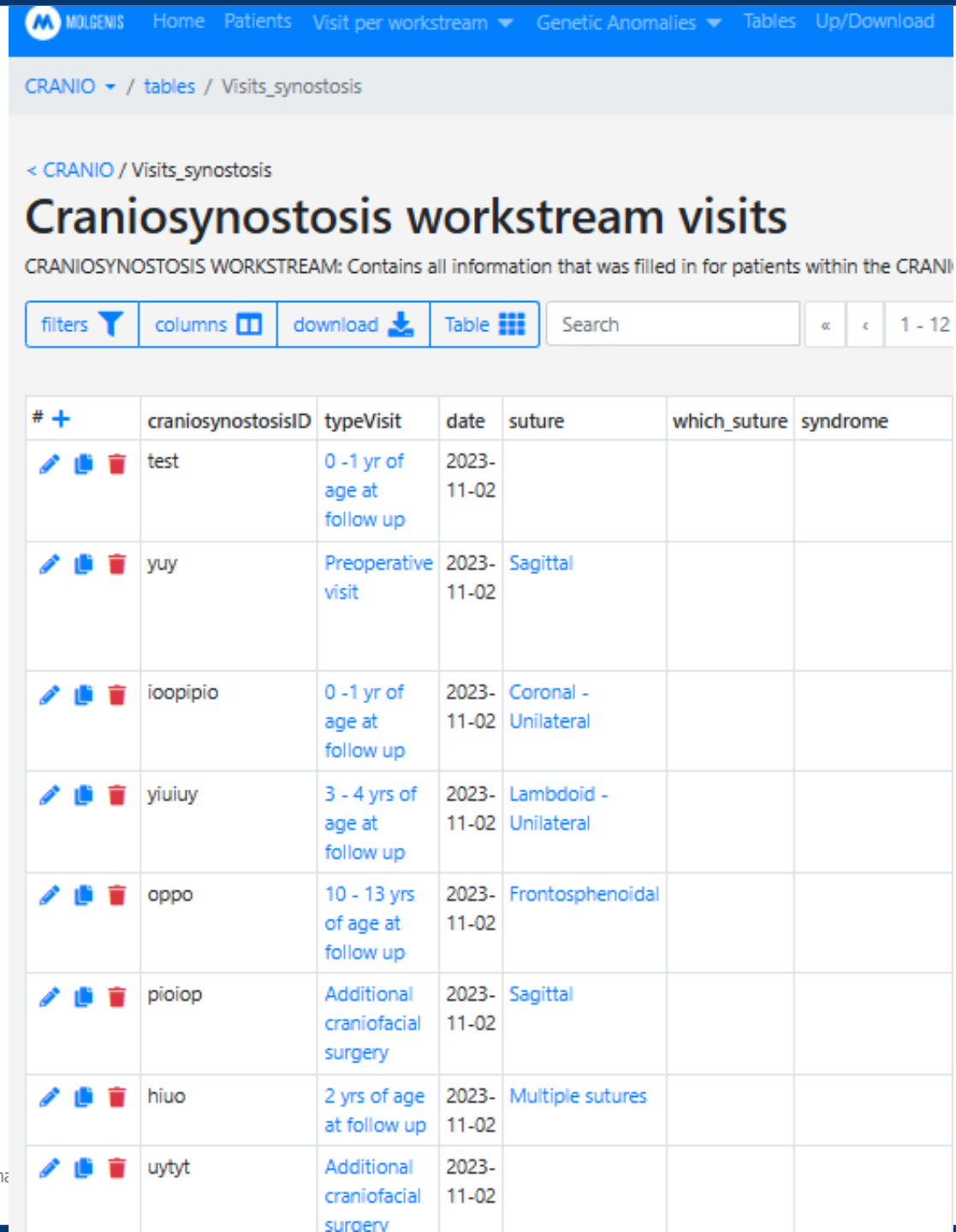
MOLGENIS

REGISTRY UPDATES

- More user-friendly
- Visits coupled to patients automatically
- Automatic calculations
- SPIDER implemented



# +	craniosynostosisID	typeVisit	date	suture	which_suture	syndrome
	test	0 -1 yr of age at follow up	2023-11-02			
	yuy	Preoperative visit	2023-11-02	Sagittal		
	ioopipio	0 -1 yr of age at follow up	2023-11-02	Coronal - Unilateral		
	yiuiuy	3 - 4 yrs of age at follow up	2023-11-02	Lambdoid - Unilateral		
	oppo	10 - 13 yrs of age at follow up	2023-11-02	Frontosphenoidal		
	pioiop	Additional craniofacial surgery	2023-11-02	Sagittal		
	hiuo	2 yrs of age at follow up	2023-11-02	Multiple sutures		
	uytyt	Additional craniofacial surgery	2023-11-02			

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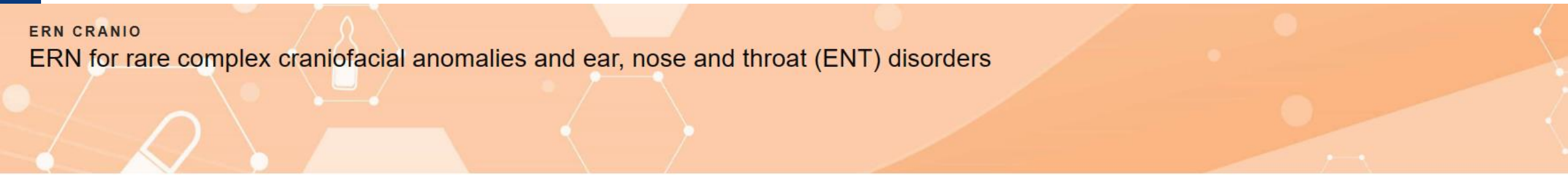
NEW HOMEPAGE AND DASHBOARD



Welcome to ERN CRANIO Registry

The **ERN CRANIO** registry is the European registry focused on the outcome of treatment using standardised diagnosis specific outcome sets (starting with craniosynostosis and cleft lip/palate) - including patient reported outcome measures and outcomes on patients' quality of life.

About
Learn more about the ERN Cranio registry
READ MORE

Registry Dashboard
View a summary of the entire registry
VIEW DASHBOARD

Healthcare Provider Login
View more information about your center
VIEW PROVIDERS

Contact

In case of any questions regarding the ERN CRANIO registry, please send us an email.

CONTACT US

ERN CRANIO
HOME
ABOUT
DASHBOARD

For Members
VIEW PROVIDERS
DOCUMENTS

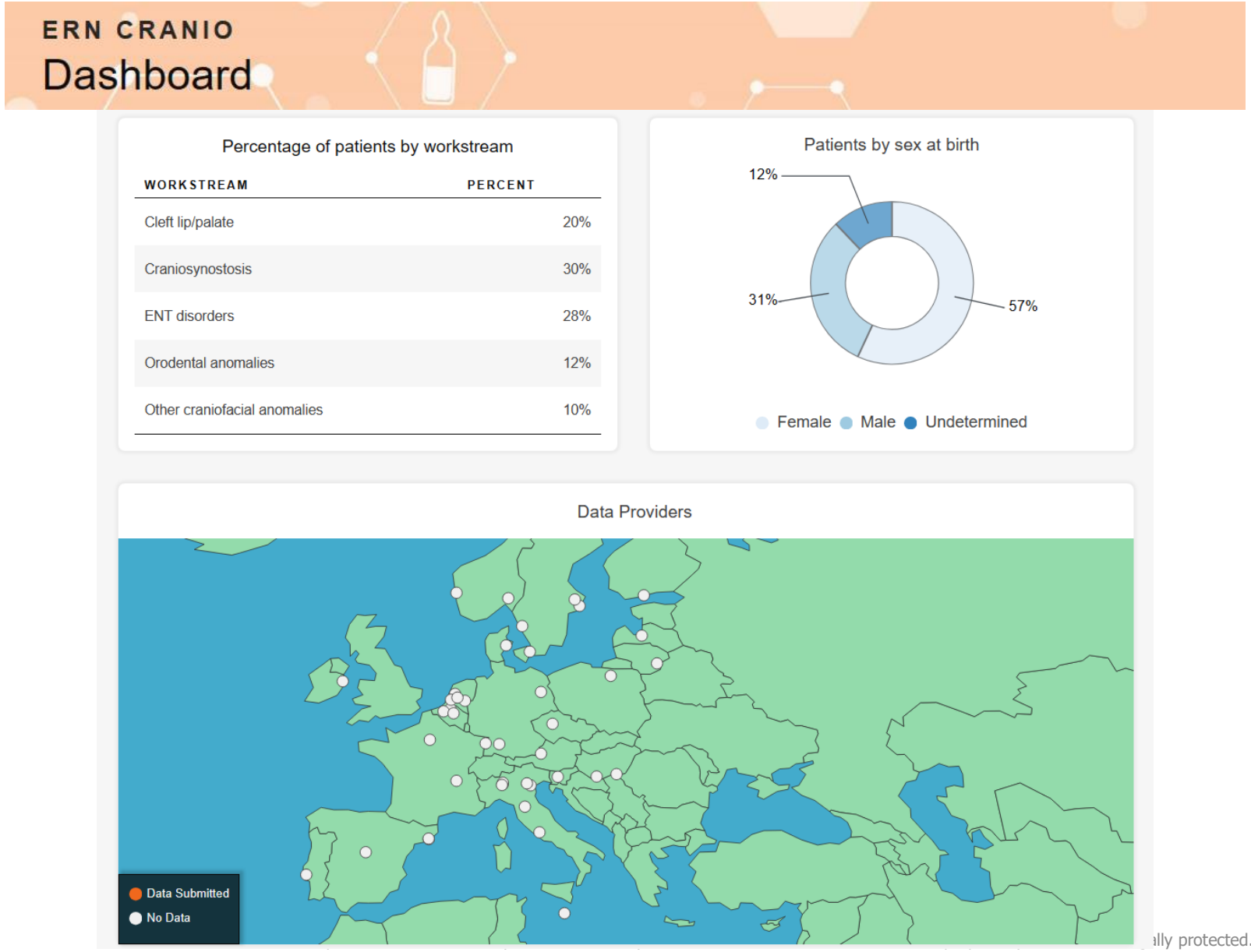
European Reference Networks | ERN CRANIO

MOLGENIS

This database was created using MOLGENIS open source software using version v8.223.0-SNAPSHOT

European Reference Network
for rare or low prevalence complex diseases
Network
Craniofacial anomalies and ear, nose and throat disorders (ERN CRANIO)

DASHBOARD – PUBLIC OVERVIEW



Your ERN logo here

ally protected.

DASHBOARD – CENTER-SPECIFIC

Dashboards

- Your center
- Craniosynostosis
- Cleft lip and palate
- Genetic Deafness
- Larynxcleft

SUBMIT PATIENT

Welcome to Charité Universitätsmedizin Berlin's dashboard!

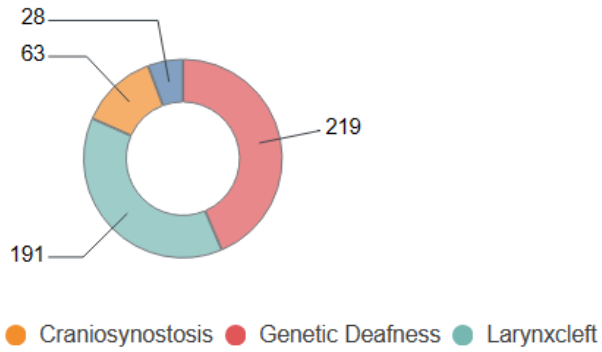
Pages are grouped by workstream. You can view an overview of patients your centre has submitted to the ERN Cranio registry, and you can compare the results of your centre against the entire registry. On the current page, you will find a snapshot of your centre as of today.

501 patients submitted

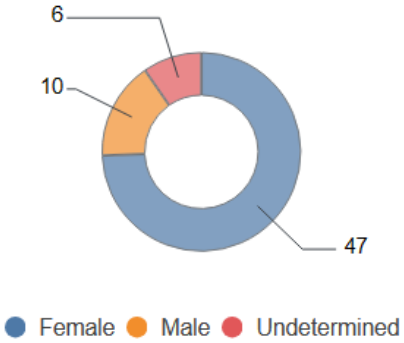
Your center has submitted on average 42 patients per month

Patients by workstream

Click a workstream to patients by sex at birth



Sex at birth for Craniosynostosis patients



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DASHBOARD – CENTER-SPECIFIC

Dashboards

- Your center
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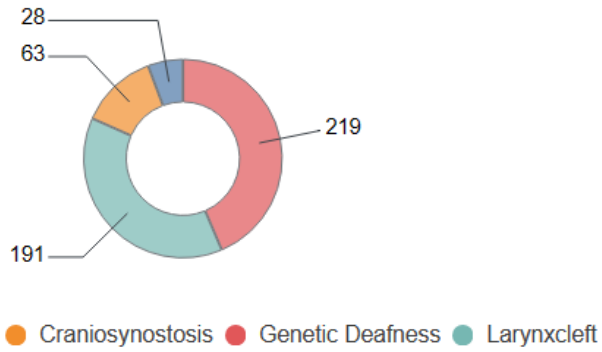

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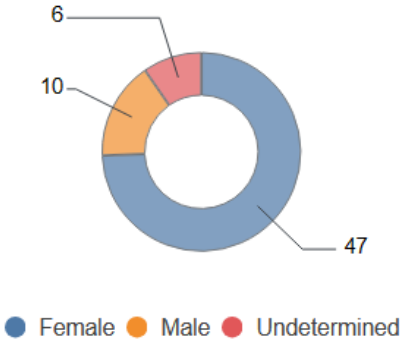

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CRANIOSYNOSTOSIS DASHBOARD – GENERAL OVERVIEW

Dashboards

- Your center
- Craniosynostosis
  - ALL CENTERS
  - General overview
  - Surgical Overview
  - YOUR CENTER
  - General overview
  - Surgical overview
- Cleft lip and palate
- Genetic Deafness
- Larynxcleft

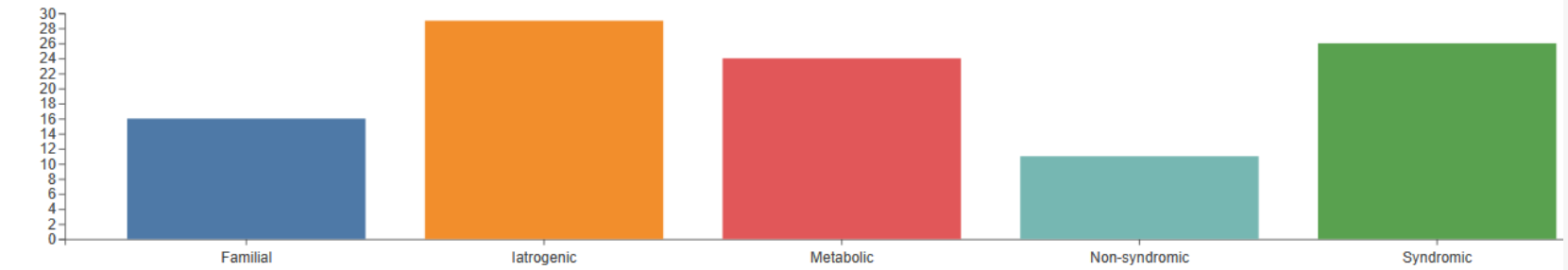
SUBMIT PATIENT

General overview for all centers

Filter data by year of birth

2023

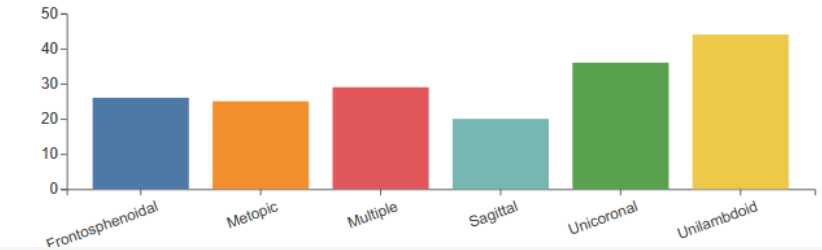
Type of craniosynostosis



Suture Overview

Click a category in the "Affected suture" chart to view more information.

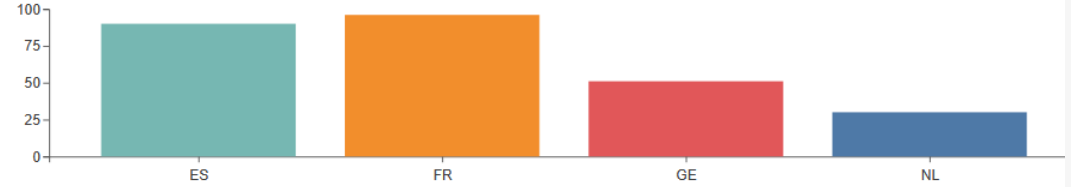
Affected suture



Patients Overview

Patients by country of residence

Total number of patients residing in each country



CRANIOSYNOSTOSIS DASHBOARD – OVERALL SURGICAL OVERVIEW

Dashboards

- Your center
- Craniosynostosis
  - ALL CENTERS
    - General overview
    - Surgical Overview
  - YOUR CENTER
    - General overview
    - Surgical overview
- Cleft lip and palate
- Genetic Deafness
- Larynxcleft

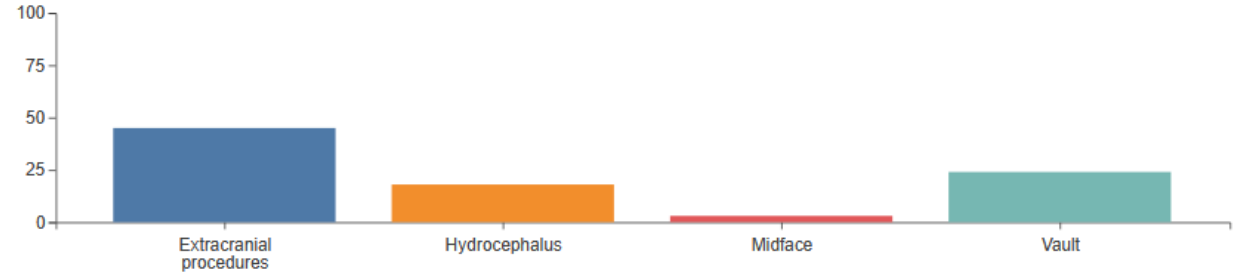
SUBMIT PATIENT

Surgical overview for all centers

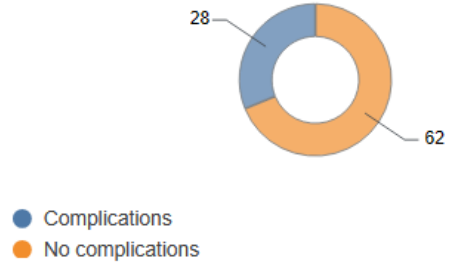
Overview of all surgical interventions

Type of surgery

Click a type of surgery to view complications



All surgical complications

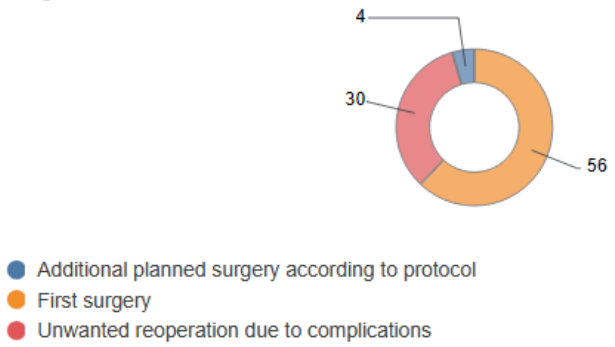


Surgical interventions by diagnosis

Select a diagnosis

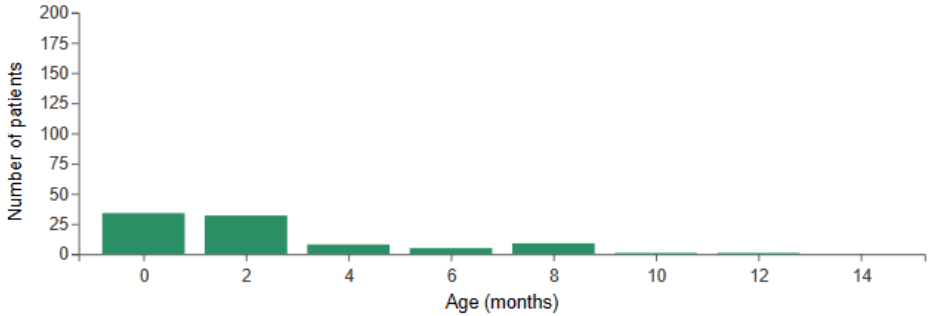
Apert syndrome

Surgical Interventions



Age at first surgery

Number of patients by age (months)



CRANIOSYNOSTOSIS DASHBOARD – GENERAL OVERVIEW OF YOUR CENTER

Dashboards

Your center

Craniosynostosis

ALL CENTERS

General overview

Surgical Overview

YOUR CENTER

General overview

Surgical overview

Cleft lip and palate

Genetic Deafness

Larynxcleft

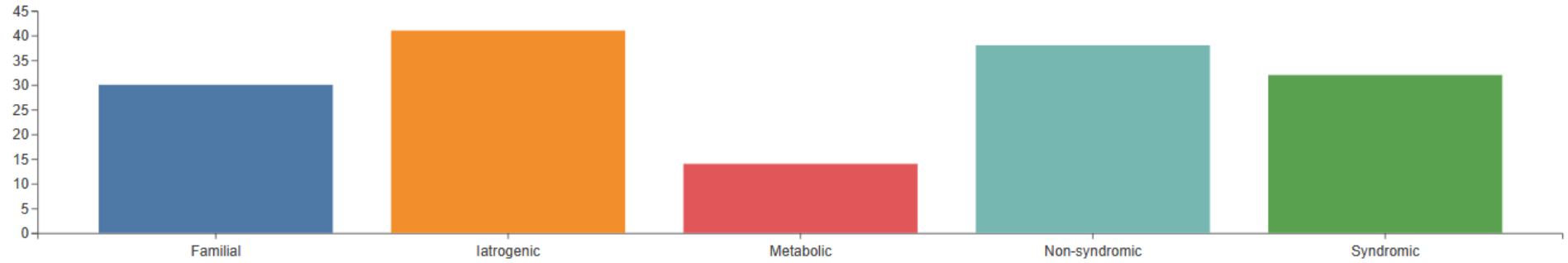
SUBMIT PATIENT

General overview for your center

Filter data by year of birth

2023

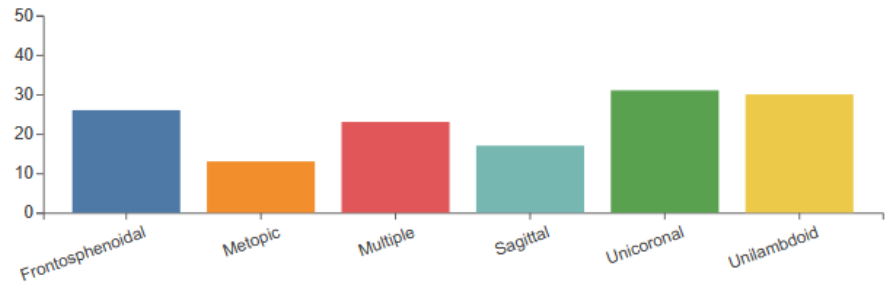
Type of craniosynostosis



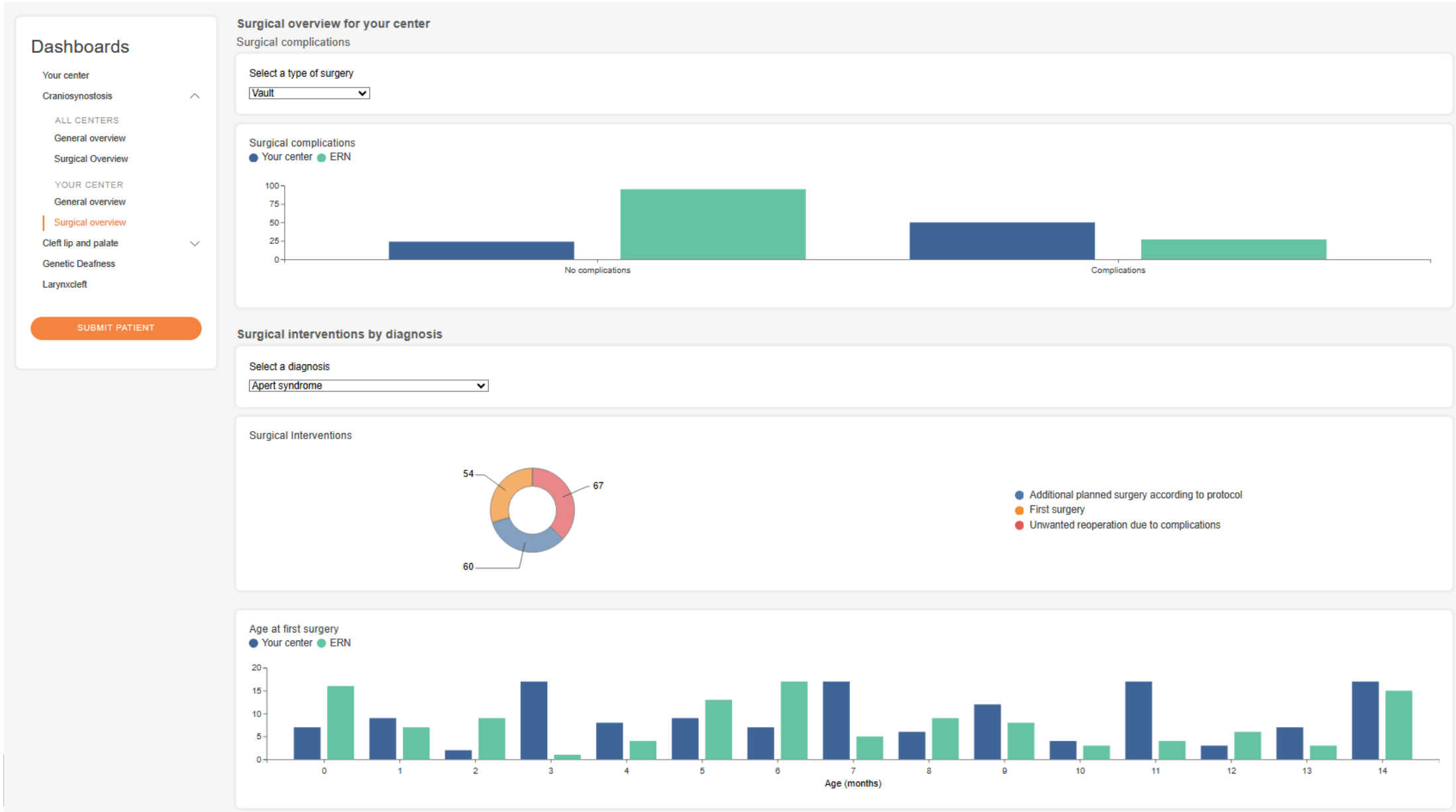
Suture Overview

Click a category in the "Affected suture" chart to view more information.

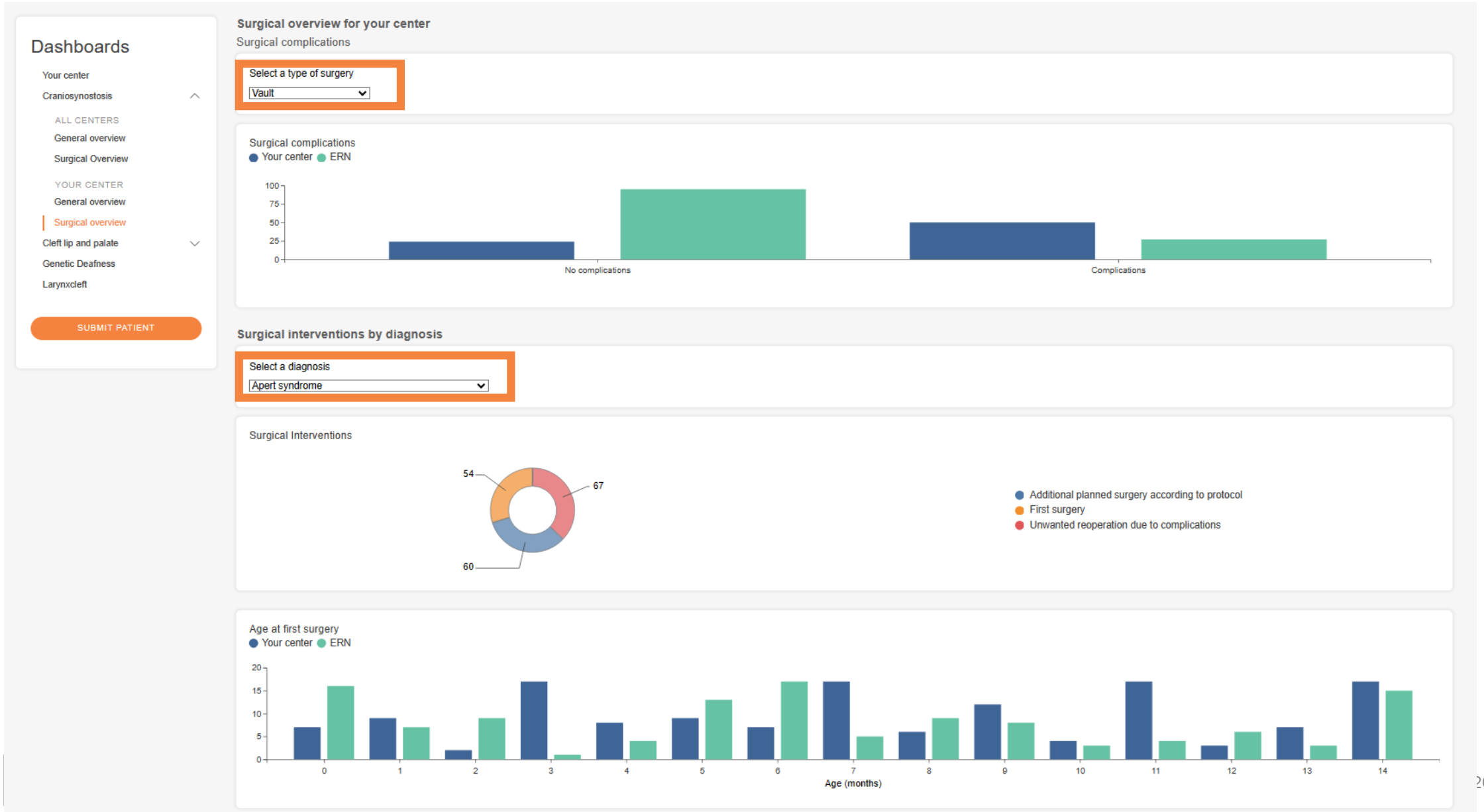
Affected suture



CRANIOSYNOSTOSIS DASHBOARD – GENERAL OVERVIEW OF YOUR CENTER



CRANIOSYNOSTOSIS DASHBOARD – GENERAL OVERVIEW OF YOUR CENTER



DOCUMENTS & RESEARCH

Dashboard

Download Documents

Download additional information about the CRANIO Registry.

Data Request Form v2	docx	73.21 KB
Data Access Policy	pdf	801.96 KB
Terms of Reference	pdf	693.95 KB

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DASHBOARD ERN CRANIO

Want to have a look yourself?

- Visit: https://beta-erncranio.molgeniscloud.org/

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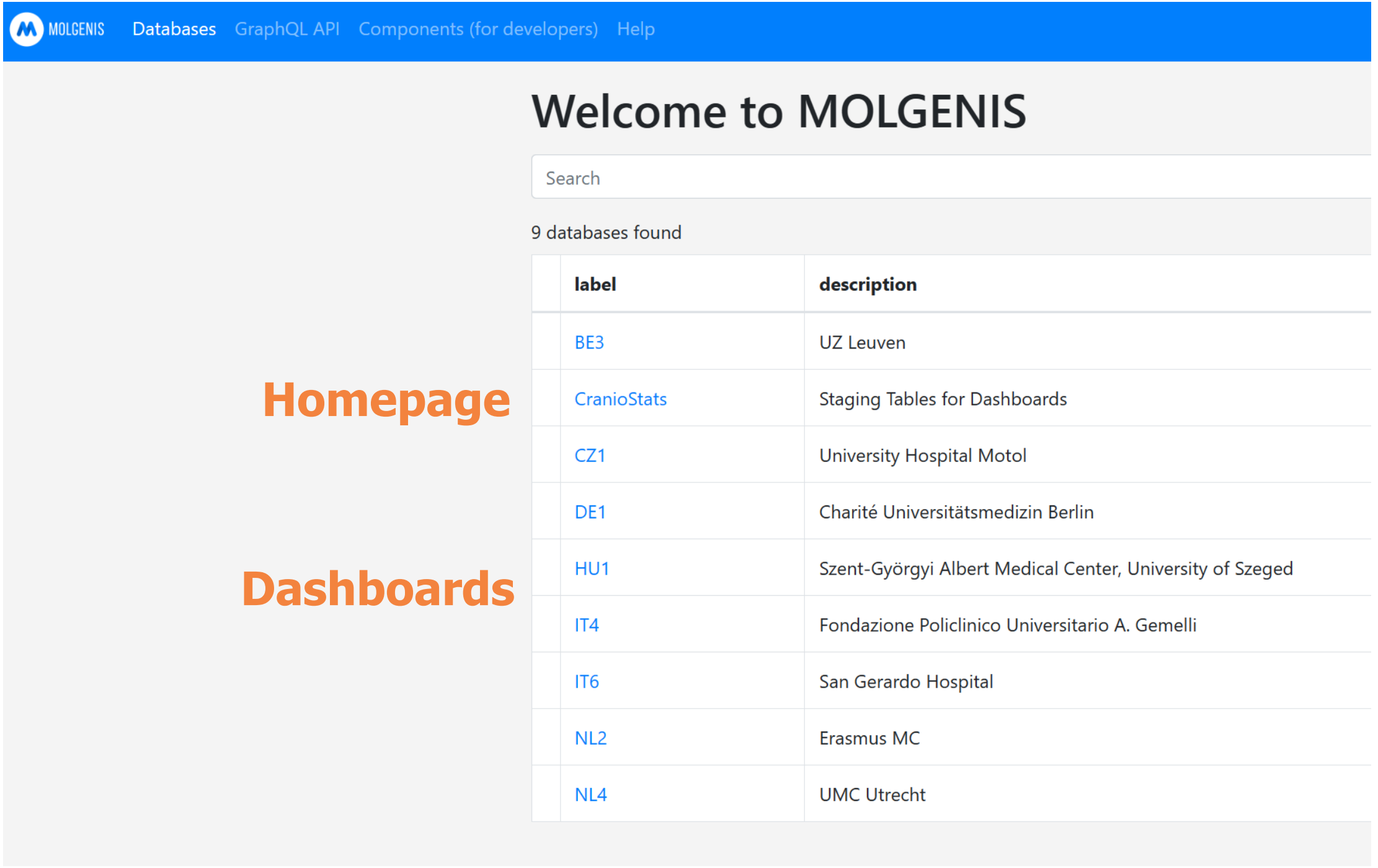

Homepage

Dashboards

Your ERN logo here

RESEARCH – UPDATE

ORIGINAL ARTICLE

A Suture-specific Photo Score for Metopic Synostosis

Gaillard, Linda MD; ERN CRANIO–Craniosynostosis Workgroup

Collaborators

Author Information

The Journal of Craniofacial Surgery ():10.1097/SCS.0000000000009773, October 10, 2023. | DOI: 10.1097/SCS.0000000000009773

OPEN SDC PAP

ORIGINAL ARTICLES

A Photo Score For Aesthetic Outcome In Sagittal Synostosis: An ERN CRANIO Collaboration

Gaillard, Linda MD; ERN CRANIO–Craniosynostosis Workgroup

Collaborators

Author Information

The Journal of Craniofacial Surgery 34(8):p 2279-2283, November/December 2023. | *DOI:* 10.1097/SCS.0000000000009732

OPEN SDC

Metrics

UNICORONAL SYNOSTOSIS PHOTO SCORE

- Research proposal discussed last year
- Photos for study can be shared via CPMS
- Aim to begin scoring in January 2024
- Please contact
  - L.Gaillard@erasmusmc.nl or
  - M.tjaberinga@erasmusmc.nl

The photo score:
Orbital vertical dystopia
Temporal hollowing
Abnormal shape of the forehead
Deviation of the nose
Overall phenotype

SCALE	Normal	Mild	Moderate	Severe

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RESEARCH IDEA TO PUBLICATION – ERN CRANIO

- How can you start performing research within ERN CRANIO?

Become eligible for ERN CRANIO research:

- Find participants during annual meetings
  - Workstream wide studies without patient data (e.g. questionnaire to clinicians)
- Study with patient data (without registry)
  - Only with participating centers that gave consensus for data use
- At least two ERN CRANIO centers (Ideal=from at least two countries)

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RESEARCH TOPICS

- **Annual meetings to discuss research**

- Researchers present research ideas
  - Relevance of research
  - Feasibility
  - Which centers will participate
  - Keep overview of completed and ongoing research

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CONTACT

- Questions on the registry or dashboard
  - **ern-cranioregistry@erasmusmc.nl**

- Photo score study
  - **M.Tjaberinga@erasmusmc.nl**
  - **L.Gaillard@erasmusmc.nl**

Dashboard link

https://beta-erncranio.molgeniscloud.org/

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Centre de Référence des Craniosténoses et Malformations Craniofaciales
CRANIOST

European Reference Networks
ERN CRANIO

FILIÈRE SANTÉ MALADIES RARES
TeteCou
MALFORMATIONS RARES TÊTE COU DENTS

3D Technician Meeting

ERN Cranio

Tareq ABDEL ALIM, Guido DE JONG, Maxime TAVERNE

Leads of the 3D Working Group – ERN Cranio

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Necker ENFANTS MALADES
HÔPITAL UNIVERSITAIRE

Radboudumc university medical center

3DLab Radboudumc

Erasmus MC
Universitair Medisch Centrum Rotterdam

Université Paris Cité

CRANIOFACIAL GROWTH AND FORM
Hôpital Universitaire Necker - Enfants Malades

Agenda

Contents

- 3D working group & questionnaire (subset)
- Endpoints of the protocol
- Guideline / Flowchart: rough outline & mandatory and flexible requirements
- Technician meeting 16/Nov/2023
- Discussion

3D Working Group & Questionnaire

3D working group

Prime objective:
Lay down best practices and standardize data acquisition and processing for facilitating seamless execution of large multi-center studies.

Aim questionnaire:
Identify key approaches and differences in current standards, which may, to a greater or lesser extent, influence the outcomes of collaborative studies.

ACQUISITION

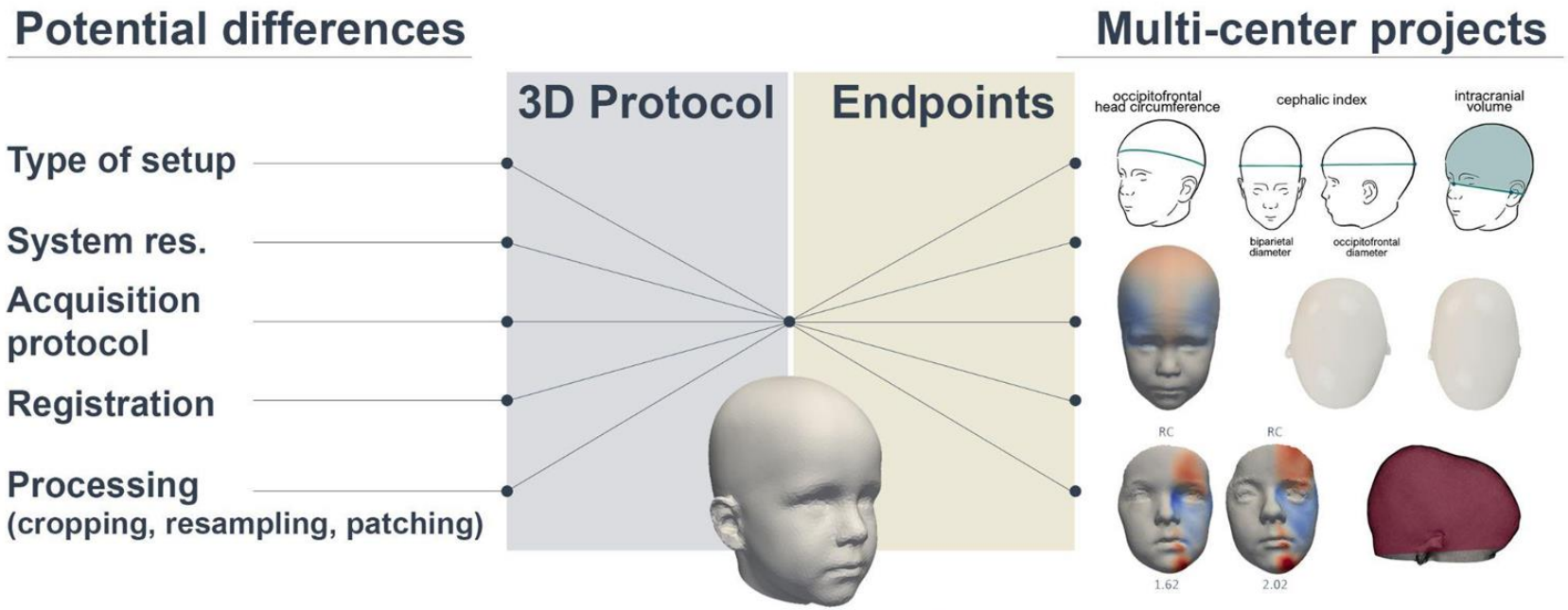
DATA STORAGE

PREPROCESSING

ANALYSIS

MULTICENTRE ENDPOINTS

3D working group



Converges to an agreed upon data structure

- ACQUISITION
- DATA STORAGE
- PREPROCESSING
- ANALYSIS
- MULTICENTRE ENDPOINTS

Questionnaire

Prime objective 3D working group:
Lay down best practices and standardize data acquisition and processing for facilitating seamless execution of large multi-center studies.

Aim questionnaire:
Identify key approaches and differences in current standards, which may, to a greater or lesser extent, influence the outcomes of collaborative studies.

ACQUISITION

DATA STORAGE

PREPROCESSING

ANALYSIS

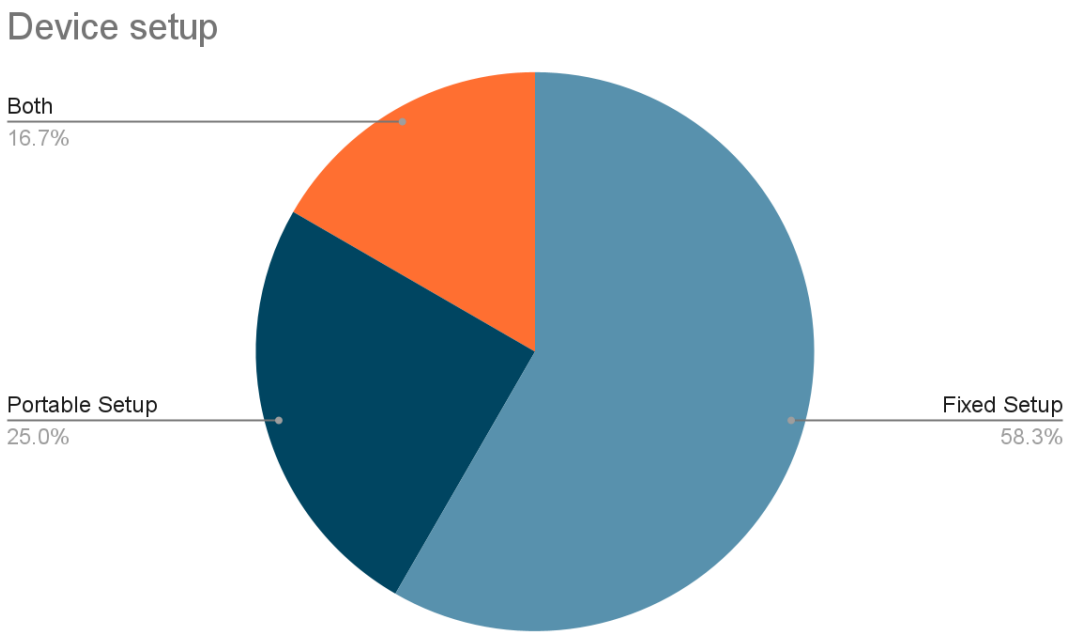
MULTICENTRE ENDPOINTS

Questionnaire - Acquisition

Motivation

Hardware

Personnel



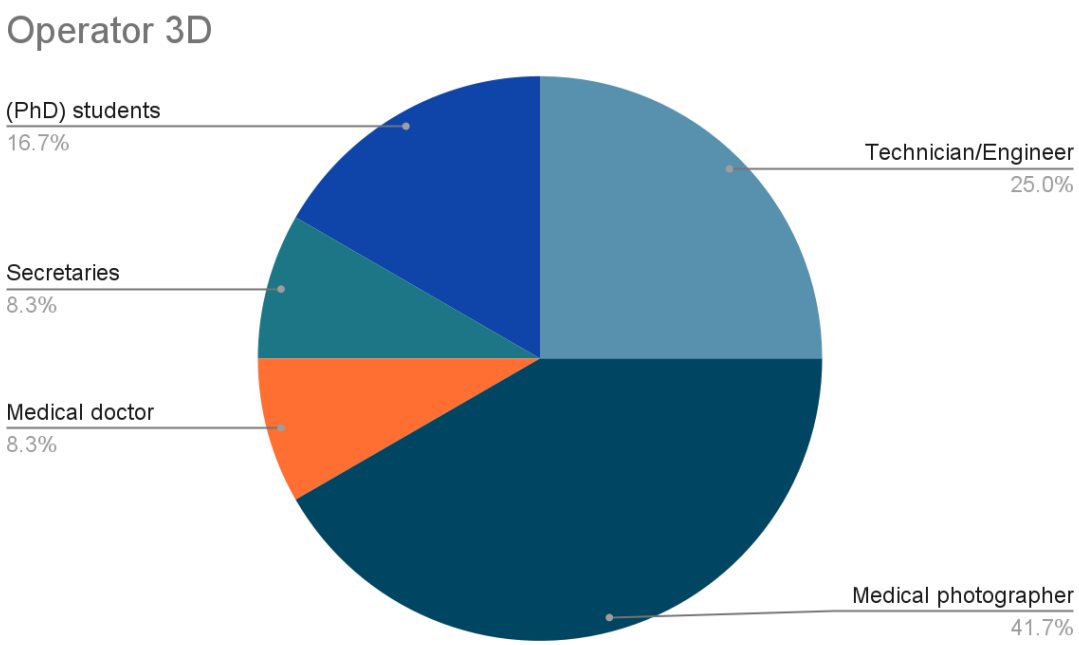
First study on validation, instead of exclusion.

Questionnaire - Acquisition

Motivation

Hardware

Personnel



Limitation 3D : you need someone for consistency, understands 3D data, integrate within your patient file.

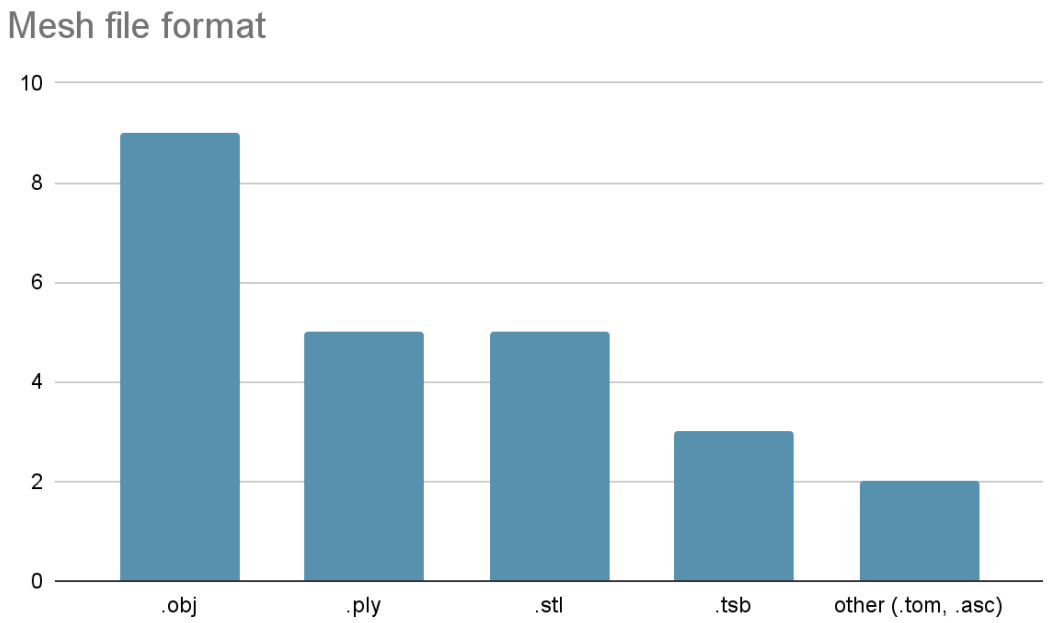
Tip: keep personnel involved to improve quality and consistency.

ACQUISITION
DATA STORAGE
PREPROCESSING
ANALYSIS
MULTICENTRE ENDPOINTS

Questionnaire – Data storage

Data format

Accessibility



Recommendation:

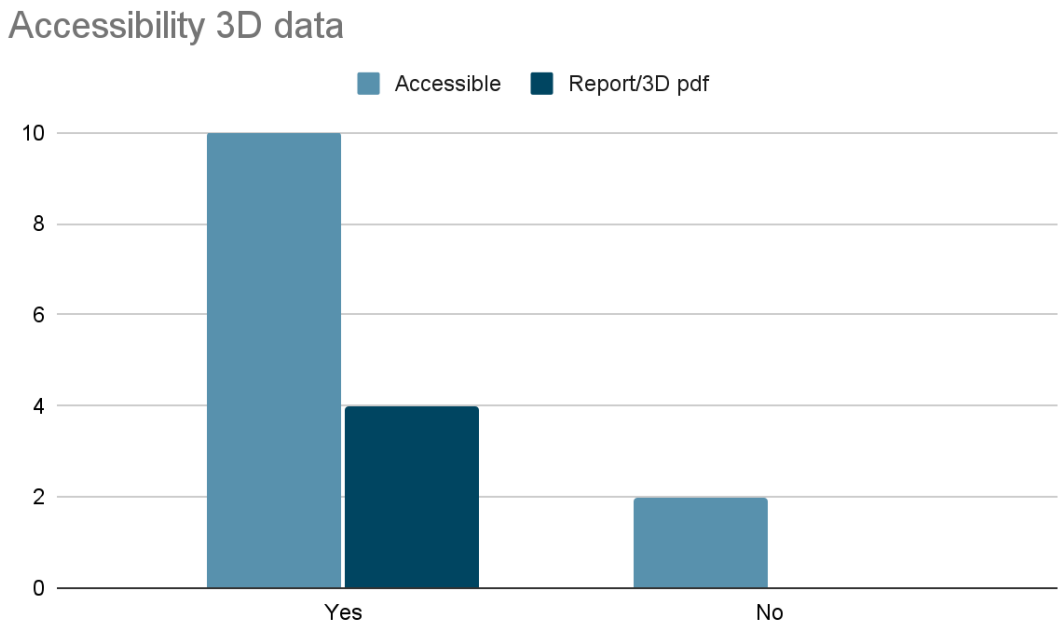
If you have the option to choose an output format use **.obj** or **.ply**

Widely used format, possibility to embed texture information

Questionnaire – Data storage

Data format

Accessibility to clinicians?



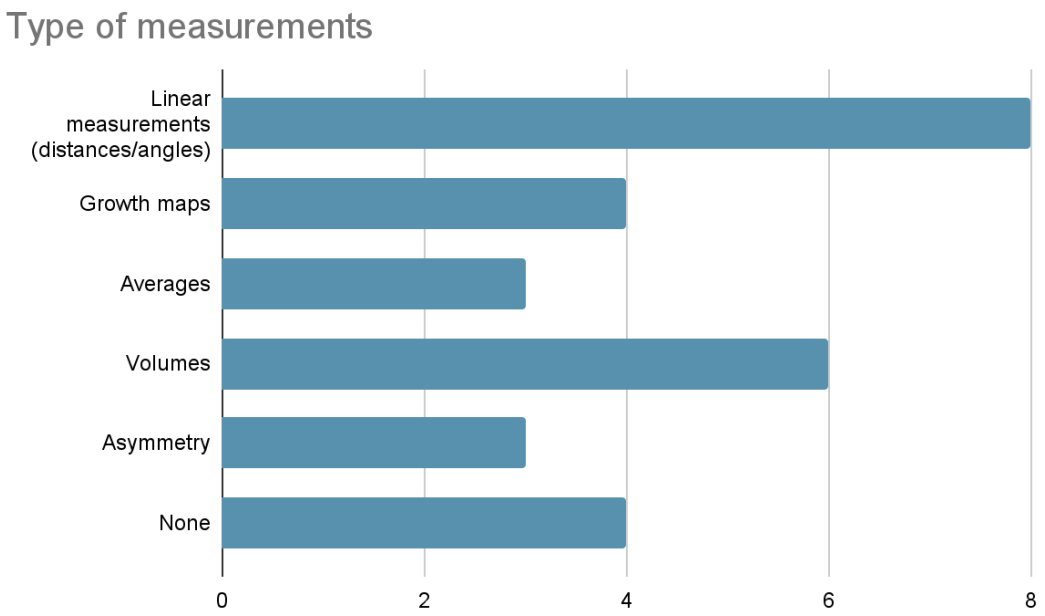
Further investigation:
Talk to your local IT department to inform about options to integrate 3D data within electronic patient records, still limited in almost all centers.

ACQUISITION
DATA STORAGE
PREPROCESSING
ANALYSIS
MULTICENTRE ENDPOINTS

Questionnaire – Analysis

Current measurements

Implications on clinical decision-making



ACQUISITION

DATA STORAGE

PREPROCESSING

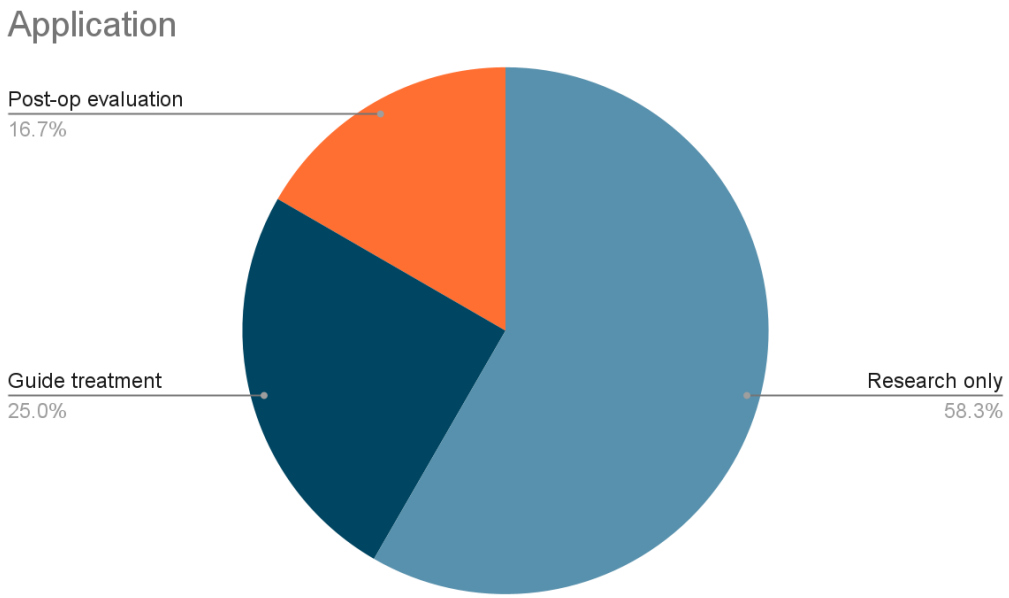
ANALYSIS

MULTICENTRE ENDPOINTS

Questionnaire – Analysis

Current measurements

Implications on clinical decision-making



Mainly limited to research

ACQUISITION

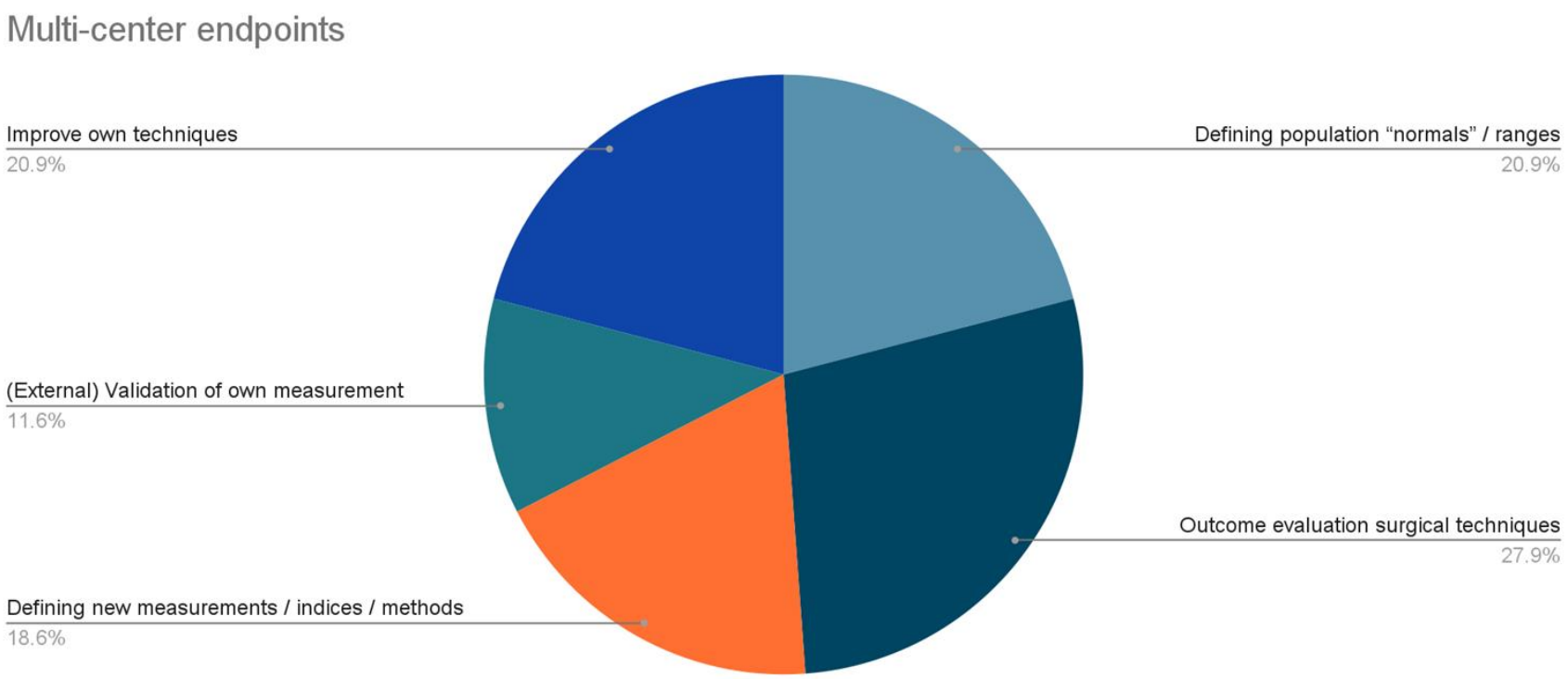
DATA STORAGE

PREPROCESSING

ANALYSIS

MULTICENTRE ENDPOINTS

Questionnaire – Multicentre endpoints



ACQUISITION
DATA STORAGE
PREPROCESSING
ANALYSIS
MULTICENTRE ENDPOINTS

Endpoints of the Protocol

Local and Global Endpoints

Local endpoints

- *Endpoints to be used internally for clinical practice and research*
- *Local Endpoints can optionally match ERN (global) endpoints or benefit from tools/data derived from these*

ERN (global) endpoints

- *(Open) Clinical and Scientific goals*
- *Collaborative Nature*
- *Provide Guidelines, Tools, and Data*

Endpoint contents

Reference endpoints

- *Define population “normal” / ranges*
- *Establish severity measures / indices*

Technique endpoints

- Development of new “measurement” techniques
- Improving of “measurement” techniques
- In/External Validation of “measurement” techniques

Evaluation (applied) endpoints

- *Evaluate surgical technique/population endpoints*
  - *To Normal*
  - *To Severity*

Endpoint contents

Reference endpoints

- *Data*

Technique endpoints

- Tools / Techniques

Evaluation (applied) endpoints

- *Application of Data, Tools & Techniques*

Endpoint contents within the ERN

Reference endpoints

- *Exchangeable, Interoperable and Future-proof Data*
- *Everyone can participate and collaborate*

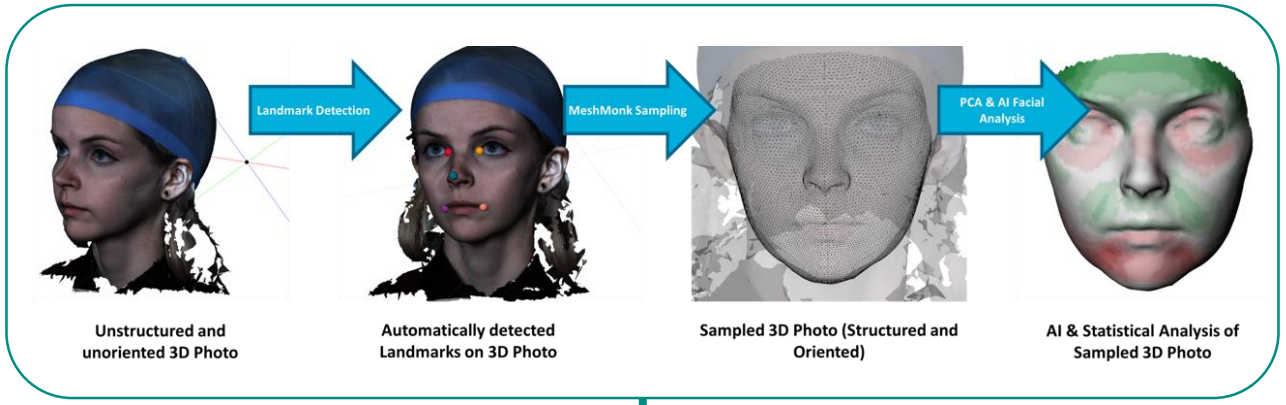
Technique endpoints

- Tools / Techniques can be created, validated and improved
- Use of the reference data

Evaluation (applied) endpoints

- *With the reference endpoints and techniques we can do collaborative research, faster, better, reproducable*

Example in Facial Analysis



Custom Database

Syndrome classification

Soha et al.
2022 IEEE Access

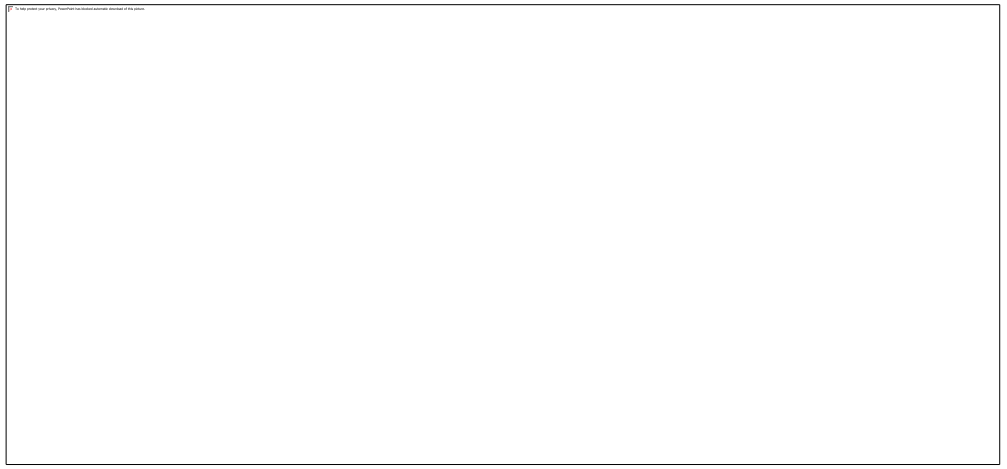
Sur. classification & Outcome Prediction

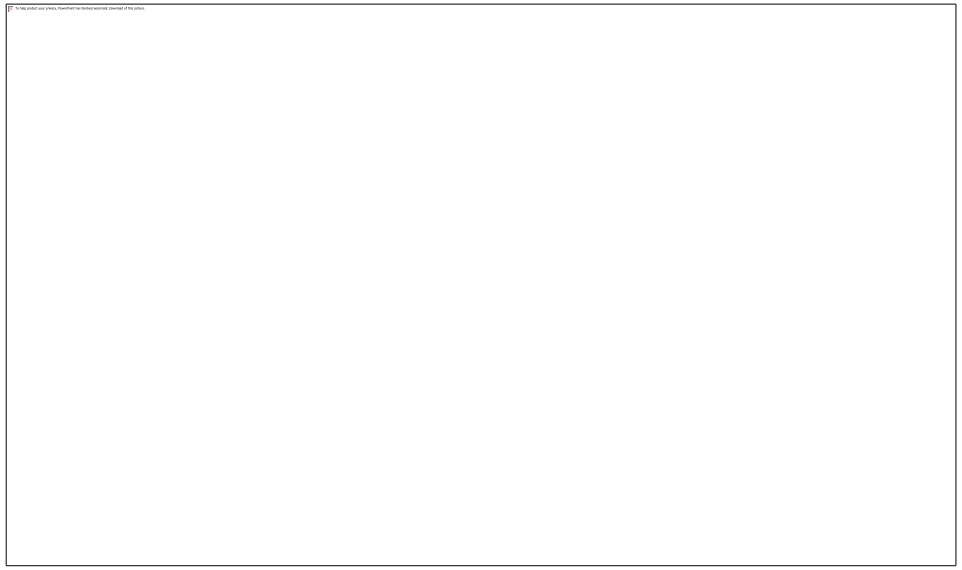
De Jong et al.
In prod.

Automatic Landmark Detection

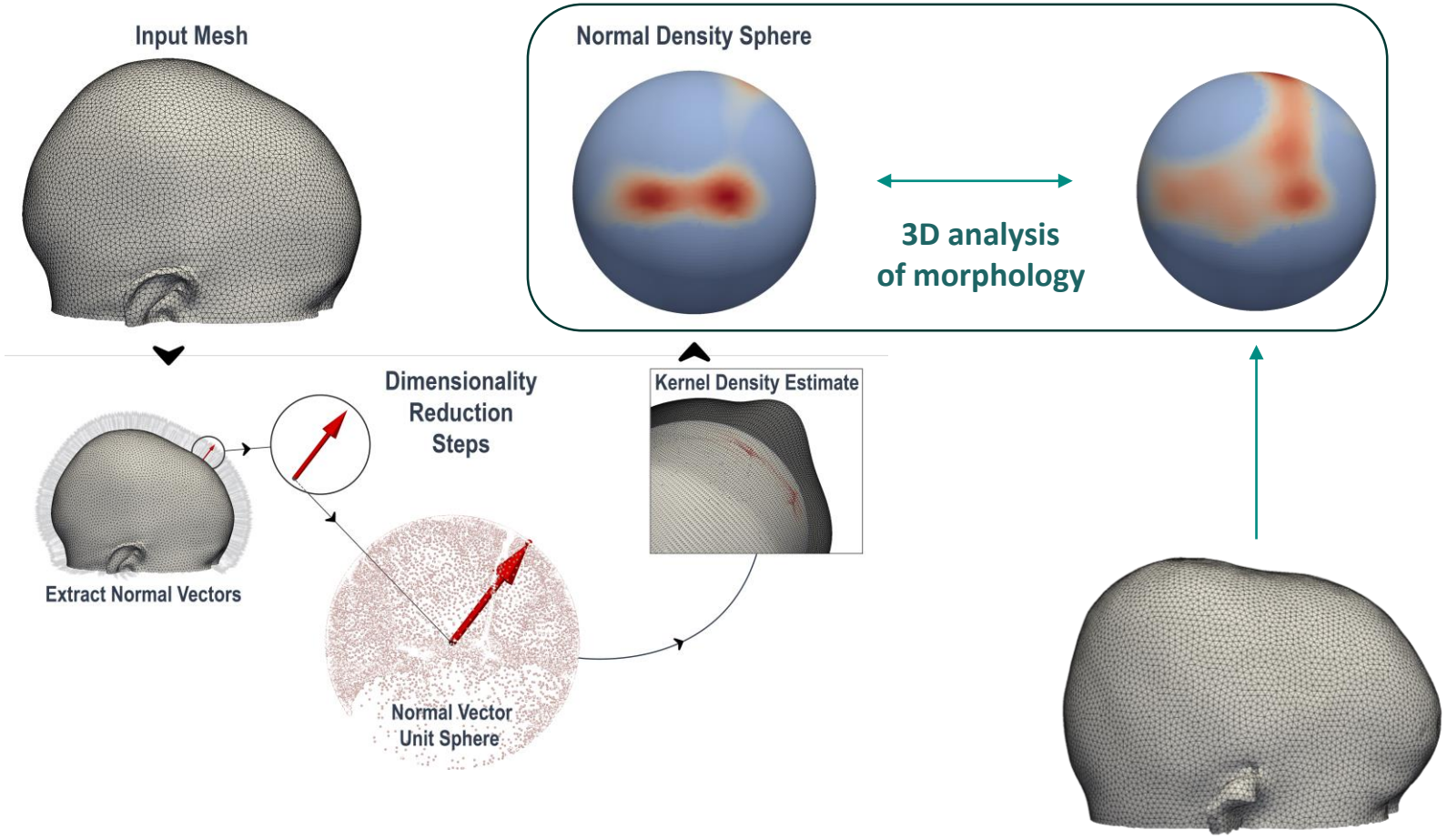
De Jong et al.
Arxiv & Submitted Manuscript

Data sharing
anonymized representations



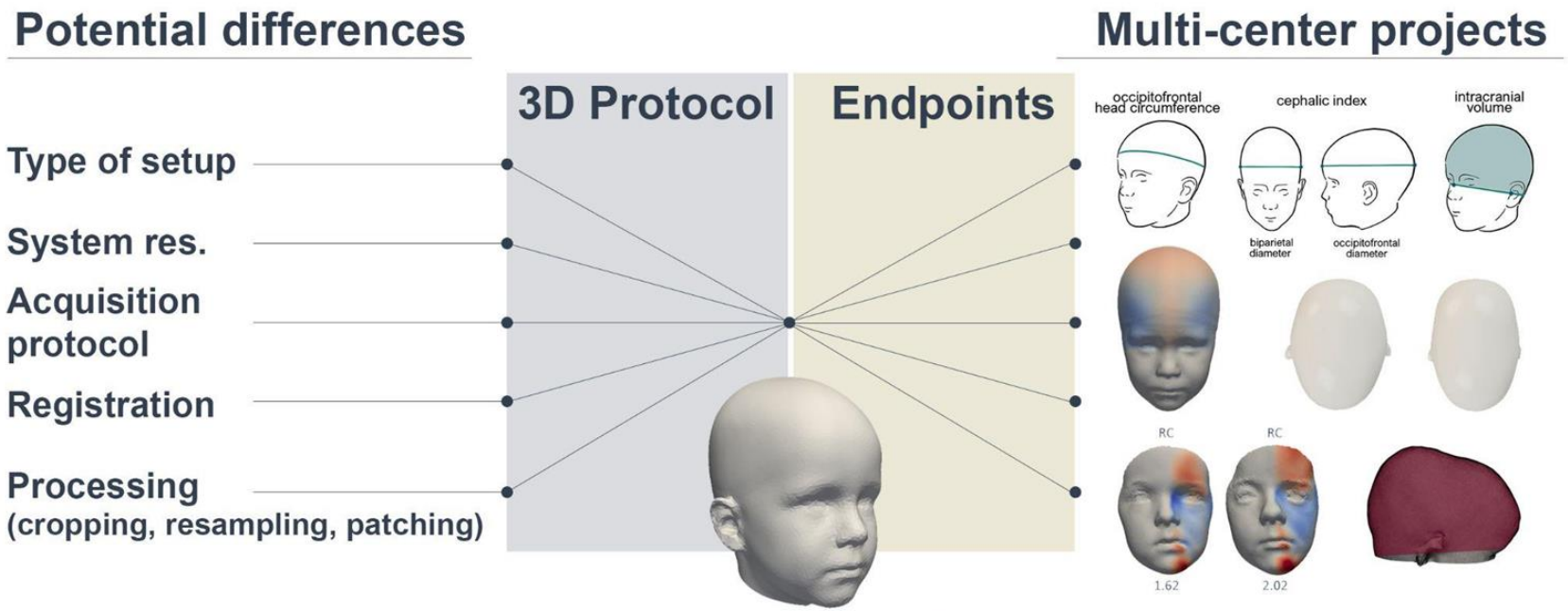


Data sharing
anonymized representations



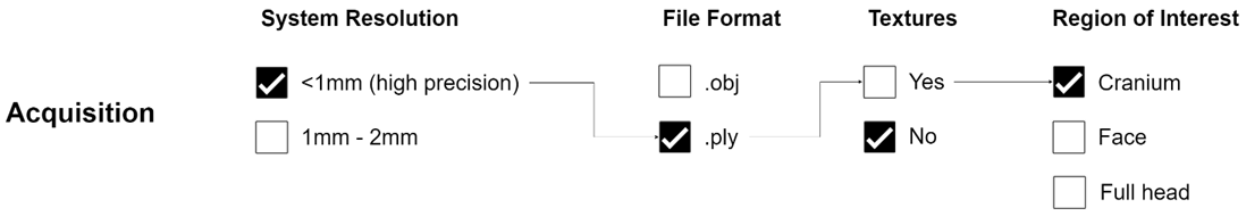
ERN Guideline / Flowchart

Flowchart



Converges to an agreed upon data structure

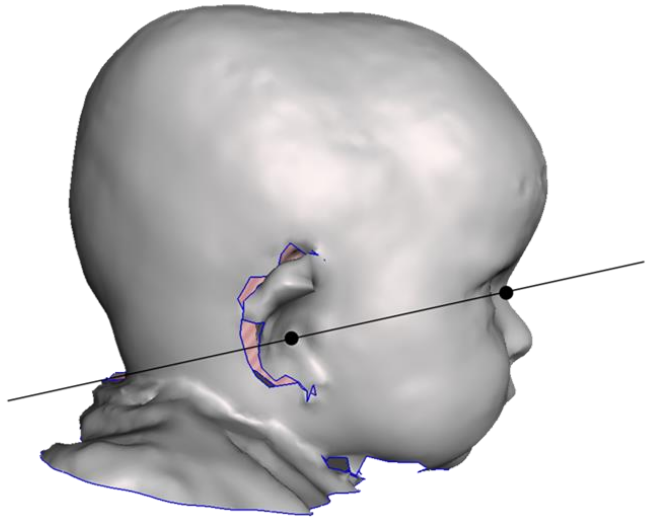
Flowchart


System Resolution
File Format
Textures
Region of Interest
Acquisition
<1mm (high precision)
1mm - 2mm
.obj
.ply
Yes
No
Cranium
Face
Full head

Flowchart

Acquisition

System Resolution	File Format	Textures	Region of Interest
☑ <1mm (high precision)	☐ .obj	☐ Yes	☑ Cranium
☐ 1mm - 2mm	☑ .ply	☑ No	☐ Face
			☐ Full head



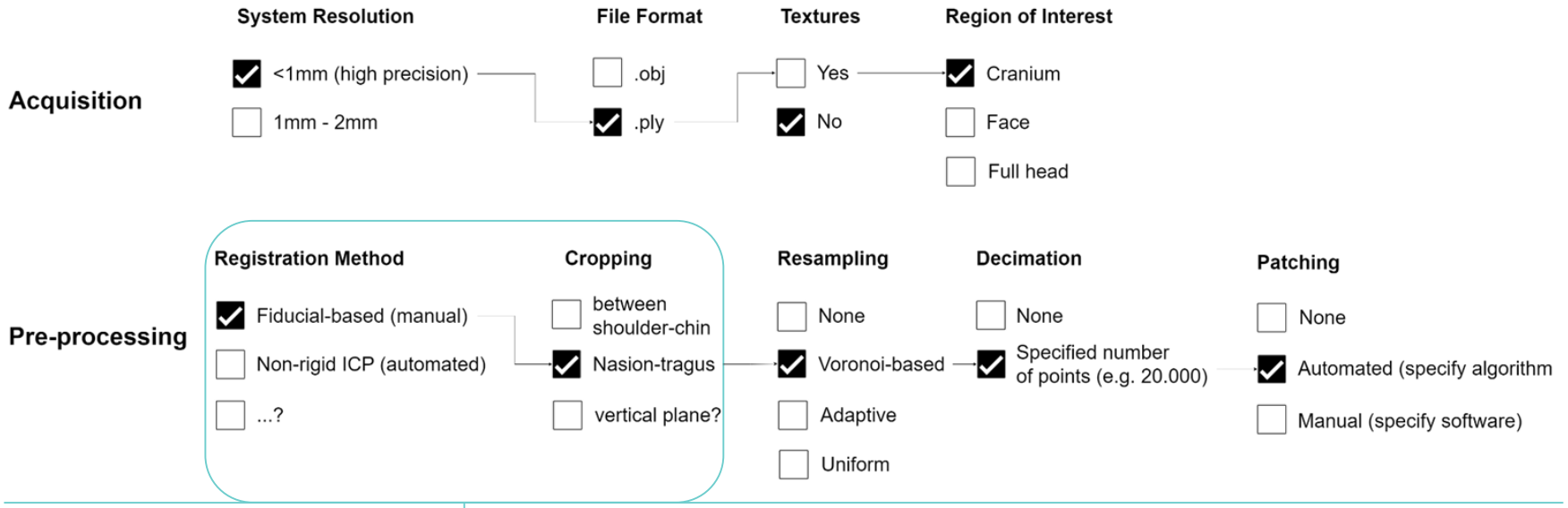
Acquisition output

Registered

Cropped

Mesh optimization

Flowchart



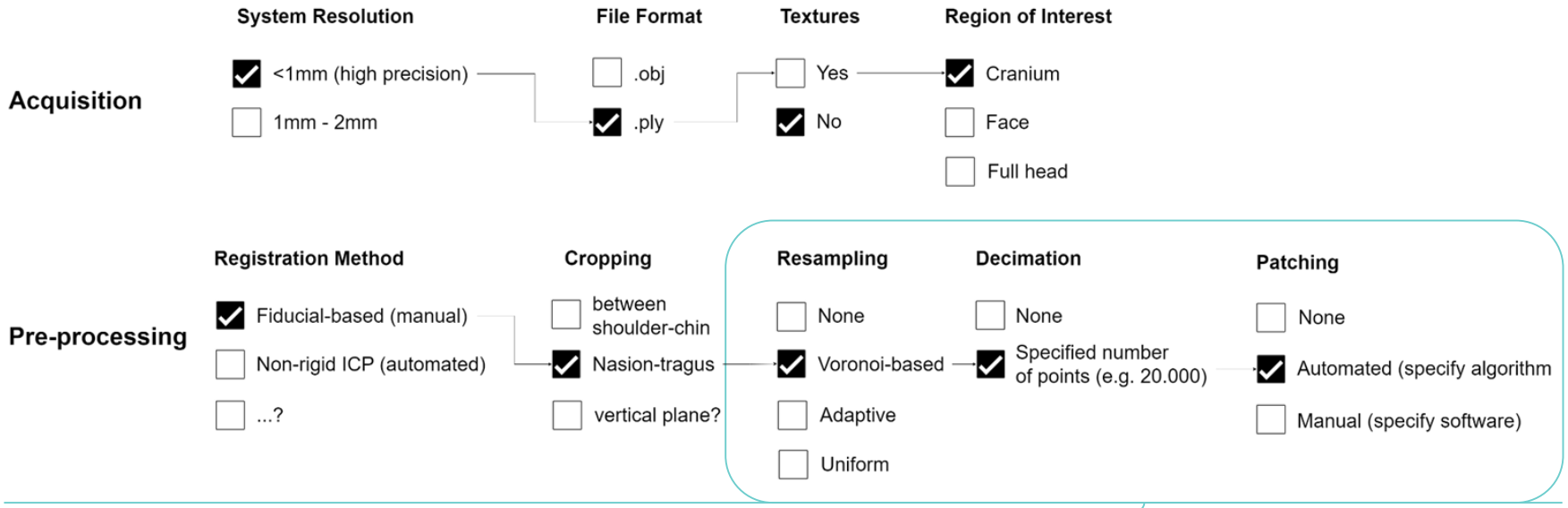
Acquisition output

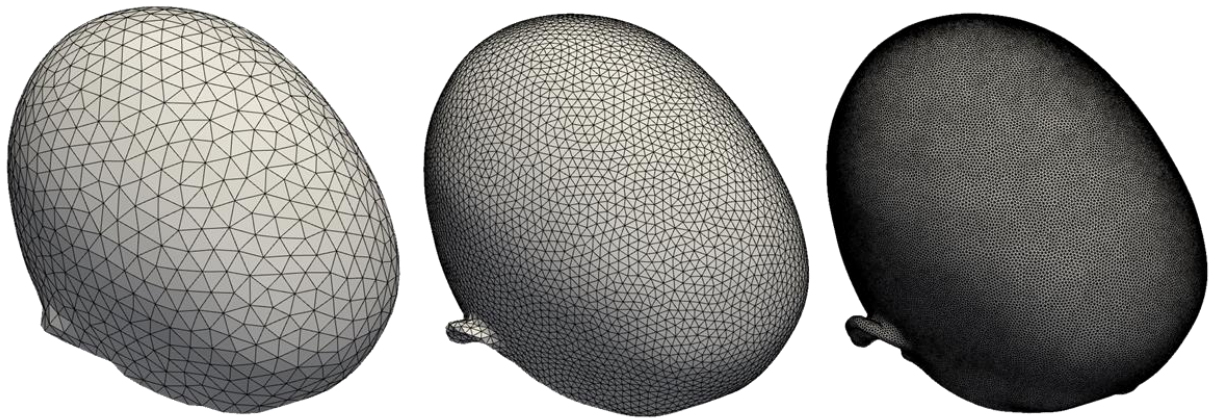
Registered

Cropped

Mesh optimization

Flowchart





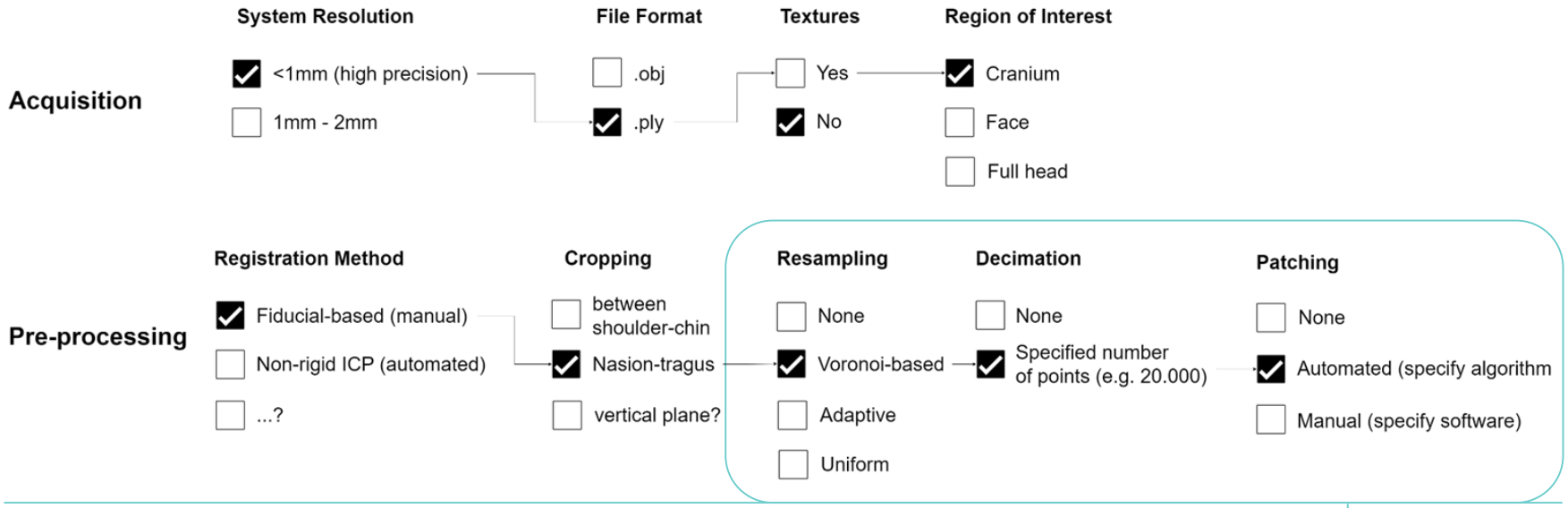
Acquisition output

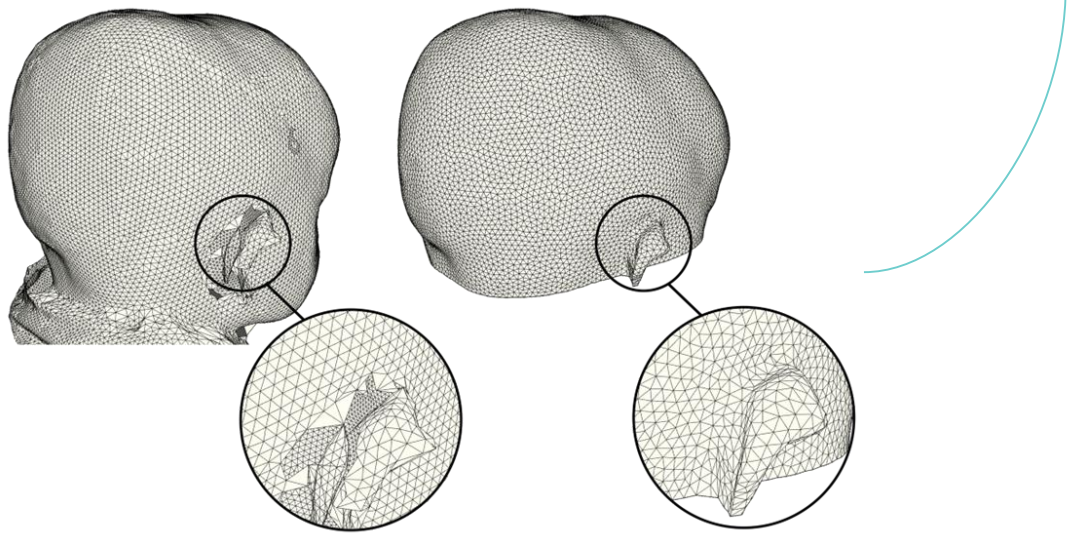
Registered

Cropped

Mesh optimization

Flowchart





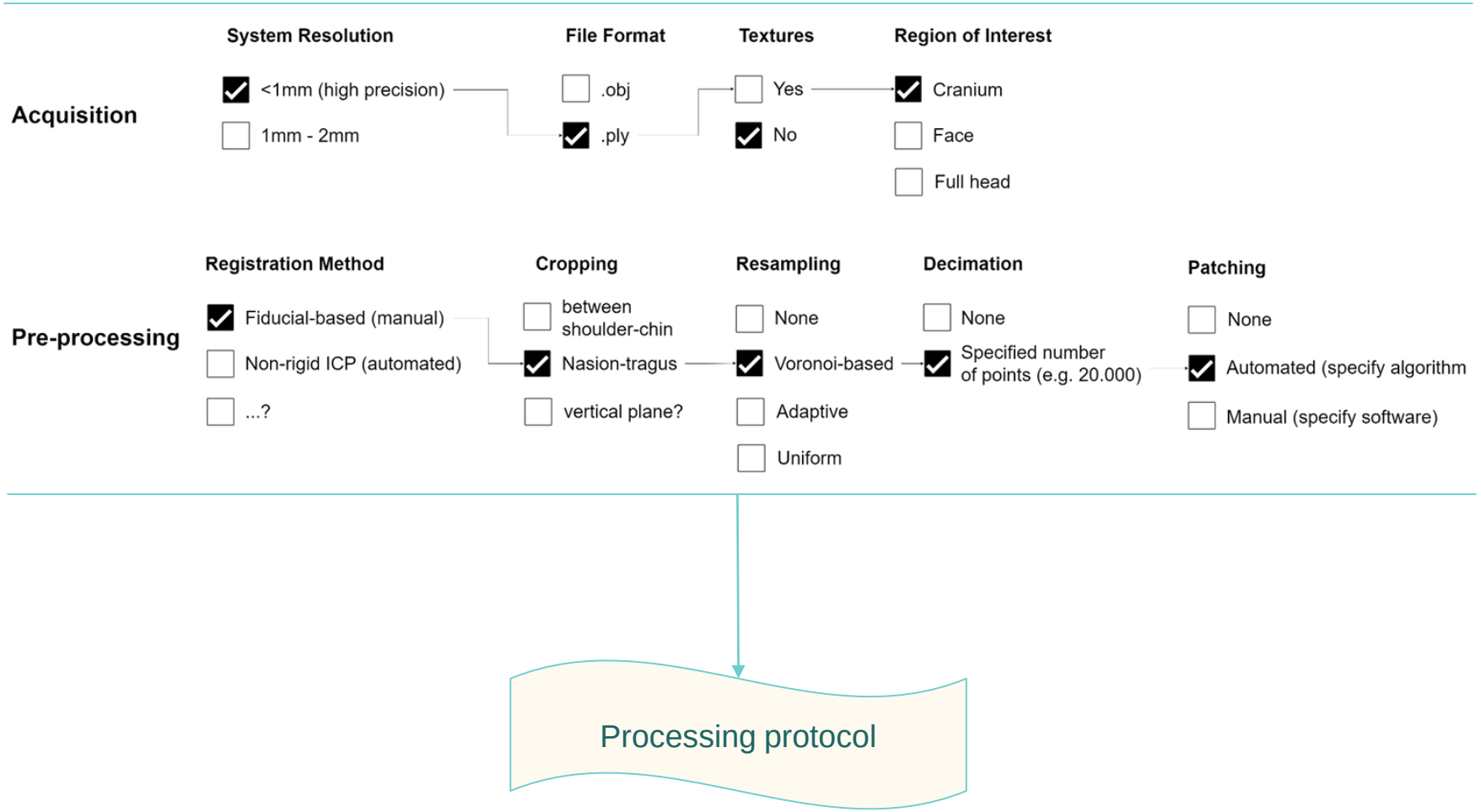
Acquisition output

Registered

Cropped

Mesh optimization

Flowchart


Acquisition
System Resolution
<1mm (high precision)
1mm - 2mm
File Format
.obj
.ply
Textures
Yes
No
Region of Interest
Cranium
Face
Full head
Pre-processing
Registration Method
Fiducial-based (manual)
Non-rigid ICP (automated)
...?
Cropping
between shoulder-chin
Nasion-tragus
vertical plane?
Resampling
None
Voronoi-based
Adaptive
Uniform
Decimation
None
Specified number of points (e.g. 20.000)
Patching
None
Automated (specify algorithm
Manual (specify software)
Processing protocol

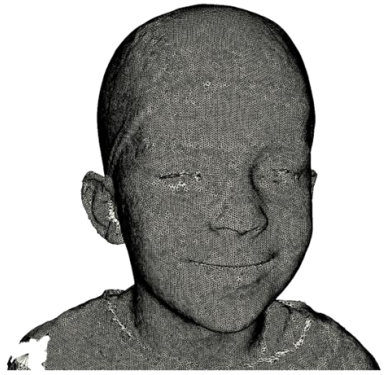
Flowchart

Acquisition

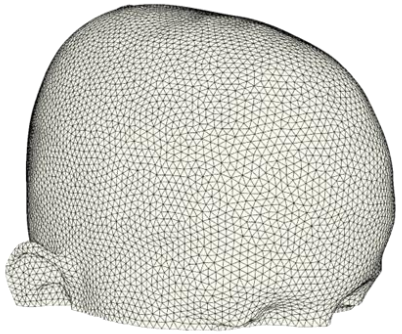
System Resolution	File Format	Textures	Region of Interest
☑ <1mm (high precision)	☐ .obj	☐ Yes	☑ Cranium
☐ 1mm - 2mm	☑ .ply	☑ No	☐ Face
			☐ Full head

Pre-processing

Registration Method	Cropping	Resampling	Decimation	Patching
☑ Fiducial-based (manual)	☐ between shoulder-chin	☐ None	☐ None	☐ None
☐ Non-rigid ICP (automated)	☑ Nasion-tragus	☑ Voronoi-based	☑ Specified number of points (e.g. 20.000)	☑ Automated (specify algorithm
☐ ...?	☐ vertical plane?	☐ Adaptive		☐ Manual (specify software)
		☐ Uniform		



Processing protocol



Technician meeting

Technician meeting outcomes 1/3

- Mainly focused on research applications, which indirectly finds its way to clinical practice fundamental findings and published results.

  Hopefully, also on direct use (e.g., surgical planning, severity assessment).
  - Need for automation of the pipeline from raw to interpretable data
  - Need for standardized data structure with attributes to ease data collection in collaborative studies. Some solution already exist in some centers (e.g., Tübingen).

- Sharing within ERN might present risks in patient's data leakage: this must be addressed in details. Especially, more control on our data may be possible if all centers use the same anonymisation method.

Technician meeting outcomes 2/3

- Maintenance of database should be anticipated on the long term. Get inspiration from already existing platforms like FaceBase.
- Consider also include 3D soft-tissue reconstruction from CT scans.
- Setting global agreement within ERN as soon as possible. Is certification mandatory in the case where data is directly used for clinical decision?
- Standardize timing of data acquisition throughout patient's management (pre, per, postop).

Technician meeting outcomes 3/3

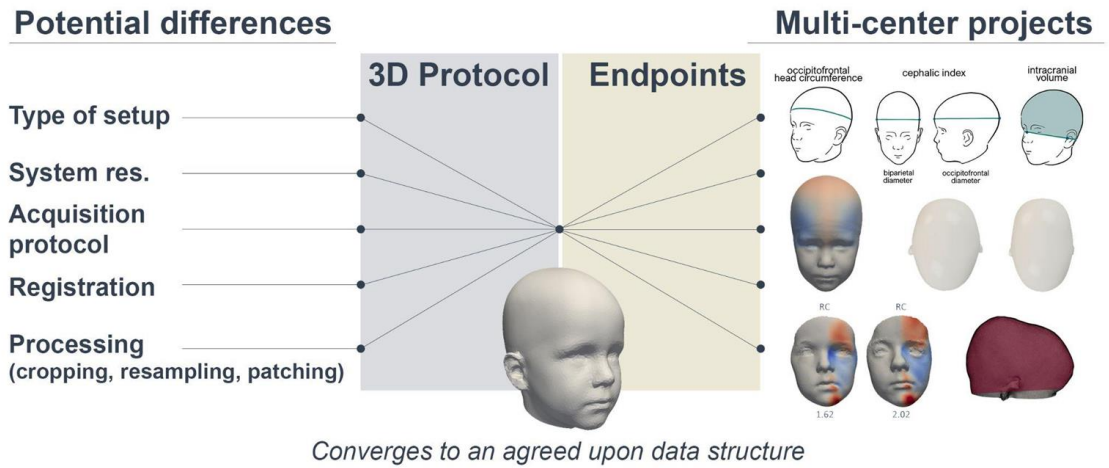
- Involve photographer (or person responsible for acquisition) in research projects
- Download files as .ply or .obj, which embed texture information
- Naming conventions, for example:
  PatientID_DoB_AcqDate [YYYY_MM_DD]
- Contact local IT dept about storage and accessibility solutions
- Storage of 3D data for clinical use could be done as 3D PDF.

Work packages 3D group

- 2024.1 Legal
- 2024.2 Research methodologies
  Registration method
  Reference planes / templates
  …
- 2024.3 Accuracy validation (different setups) collaborative paper
- 2024.4 Writing of Guidelines → aimed to present next ERN
- 2024.5 Data sharing and storage opportunities
- 2024/25 Software / tool development

Discussion

Discussion



What further endpoints do you foresee and are there topics that should be further explored collaboratively (with the technicians)?

Say that we start a collaborative project today, with 10 centers. What challenges will we face when we consider the data?

What are key steps to include we have missed or should consider?

What do you think are the most important sources of variability that may influence the outcomes?

What are key elements that you would like to see in the ERN protocol for 3D imaging?

Centre de Référence des Craniosténoses et Malformations Craniofaciales
CRANIOST

European Reference Networks
ERN CRANIO

FILIÈRE SANTÉ MALADIES RARES
TeteCou
MALFORMATIONS RARES TÊTE COU DENTS

Thank you for your contribution

Radboudumc university medical center
3DLab Radboudumc

Erasmus MC
Universitair Medisch Centrum Rotterdam

Université Paris Cité

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS
Necker ENFANTS MALADES
HÔPITAL UNIVERSITAIRE

CRANIOFACIAL GROWTH AND FORM
Hôpital Universitaire Necker - Enfants Malades

REDO SURGERY FOR SAGITTAL SYNOSTOSIS; REDO AFTER REDO

ERN Cranio Dublin

17 November 2023

INCIDENCE REDO FOR SSS IN LITERATURE

- **First redo for raised ICP: 1.4-23.5% depending on follow-up time and technique**
- **No studies on recurrent raised ICP after second cranial enlargement**

Moore et al. 2021
23.5%, 5.6%, 3.2% and 1.9% of secondary raising ICP patients who underwent the primary surgery between 1999–2004, 2005–2010, 2011–2015 and 2016–2018, respectively (p 0.024).
No details on ICP monitoring

Thomas et al. 2015
The overall incidence of raised ICP following corrective surgery for SC in this study was 6.9%; among MSC treated patients the rate was 14.6%. This is higher than the 1.4%–3.8% rate reported in other series of patients undergoing strip craniectomy.
ICP monitoring baseline consistently above 15 mmHg

Cetas et al. 2013
Five (6.2%) of 81 children with repaired, nonsyndromic, single-suture (sagittal) synostosis later presented with delayed intracranial hypertension and underwent a second cranial vault remodeling.
ICP measurements: >15mmHg

INCIDENCE REDO ROTTERDAM

1991-2022
Total operated: 749

Cranial remodeling	**17** (14 ICP increase= 1,9% (1-6% depending on technique))
Split skull graft	**13**
Repositioning springs	**1**
Completing craniotomy	**1**
Post op hemorrhage	**1**
Dural defect closure	**2**
Scar correction	**2**

Erasmus MC

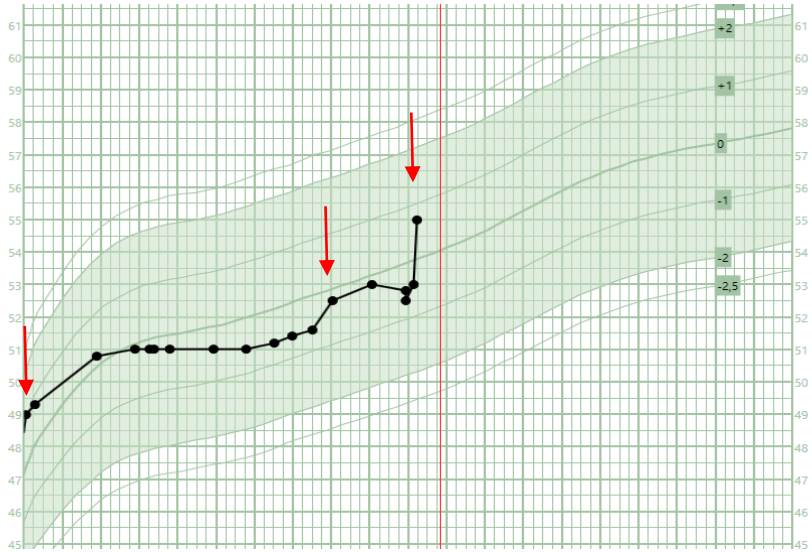
RECURRENT SYMPTOMS AFTER REDO

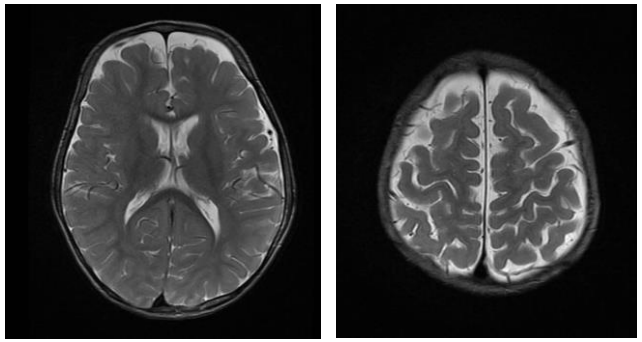
SD boy 11 y

Redo at age 14m (frontobiparietal)
for asymmetry after incomplete craniotomy (springs)
No genetic deficiencies

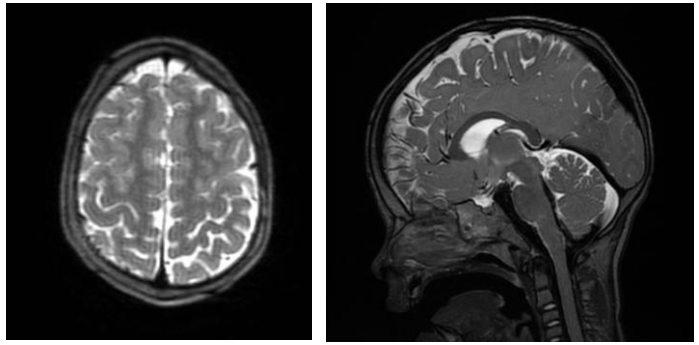
Second redo at age 8y (biparietal)
for skull growth stagnation
complaints of headache, not thriving at school
borderline ICP measurements.

Third redo at age 11 y (occipital with ext distractors)
recurrence of complaints of headache etc.





6m after first redo



5y after first redo

Erasmus MC

RECURRENT SYMPTOMS AFTER REDO

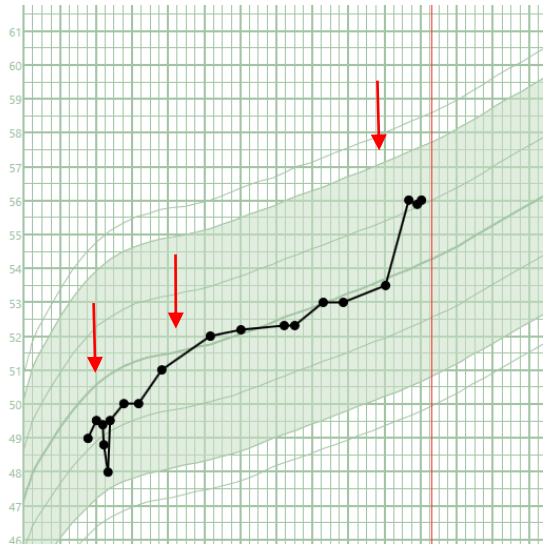
MR boy 12 y

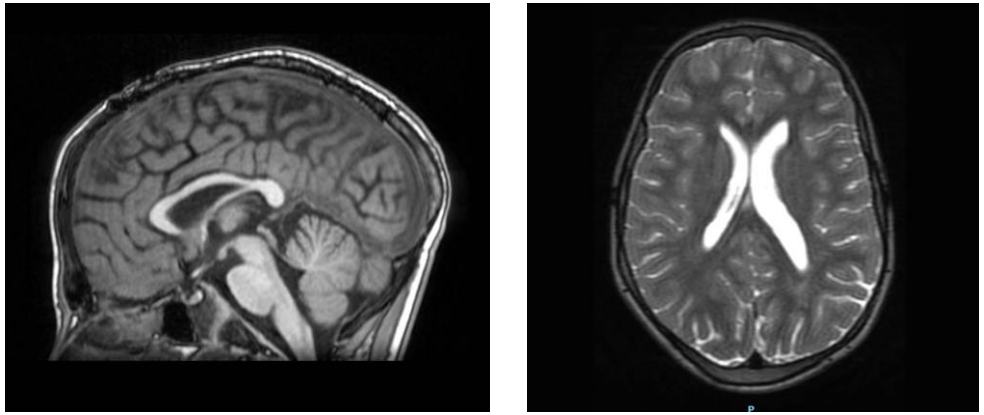
Redo at age 3y (frontobiparietal)
- After endoscopic strip and cosmetic redo elsewhere
- Fontanel buldge, papilledema
- 10p13 deletion of unknown relevance

Second redo at age 5y (biparietal)
- for skull growth stagnation
- complaints of headache, not thriving at school
- borderline ICP measurements.

Third redo at age 10 y (occipital with ext distractors)
- postop perfect
- after 1 ½ yr recurrence of complaints of headache etc.

ICP: prone 10-15 mmHg, at end of the night 20mmHg
3 REM peaks 10 minutes, 20-30mmHg





MRI at age 12

Erasmus MC

RECURRENT SYMPTOMS AFTER REDO

N=3

First redo at early age for
- cosmetic reasons
- raised ICP
- (No genetic deficiencies)

Second (and third) redo for
- skull growth stagnation
- complaints of headache, not thriving at school
- borderline ICP measurements.
- *Surgery helps for 1-2 years….*

Erasmus MC

IS THIS PROBLEM RECOGNIZED?

Do other centers see comparable patients?

What could be the origin of the recurrent problems?

- wrong decision to do re-expansion?
- reduced growth due to repeated surgeries?
- too big/small enlargement at first redo?

Would it be worthwhile to collect (second) redo patients within ERN centers?

PATIENT PARTNERSHIP IN ERN CRANIO

17 November 2023

Dublin, Ireland

European Patient Advocacy Group

European Reference Network for rare or low prevalence complex diseases

Network Craniofacial anomalies and ear, nose and throat disorders (ERN CRANIO)

CONTENT

- Introduction to EURORDIS Patient Partnership Framework
- Guiding principles of the Framework
- Patient-clinician collaborations in ERN CRANIO
- Ideas for collaboration?

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Introduction to EURORDIS Patient Partnership

Patient partnership in the ERNs can be defined as a **mutual relationship** between patients and health professionals where input from people living with a rare disease or caring for someone with a rare disease **routinely and formally** informs the Networks' collaborative activities and decision-making.

Patient partnership implies considering health professionals and patients involved in the Networks as **equal partners** in all ERN activities and domains.

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GUIDING PRINCIPLES

MUTUAL RESPECT

Patients and health professionals respect each other, communicate openly, and actively listen to each other. Everyone can openly express their needs, perspectives, and concerns without fear of reprisal.

LEARNING

Patients and health professionals are open to learn about how things may improve and are open to learn from each other.

TRANSPARENCY

Patients and health professionals are transparent about knowledge gaps and about the challenges and constraints that they might face in partnering effectively in the Network.

COMPLEMENTARITY

There is a mutual recognition of the complementarity of scientific, professional, and experiential knowledge that health professionals and patients bring to the table. Both act in ways that demonstrate the value of the input provided by the other party.

SHARED LEADERSHIP

Everyone is aware of the Network's goals and feels empowered to make proposals and take the lead on projects based on their expertise. Patients and health professionals jointly shape and lead the work of the Network and have a shared responsibility for the Network's performance.

TEAMWORK

Patients and health professionals work together from the beginning to set priorities, agree on activities, identify gaps and needs, and cooperate to develop solutions and projects.

PROFESSIONALISM

Patients and health professionals live up to the commitment they have made to contribute to the Network, communicate regularly, and report on the progress of ERN-related projects.

CONTINUOUS INVOLVEMENT

Patients and health professionals work together from the beginning in all ERN collaborative activities and projects.

CLARITY OF ROLES AND RESPONSIBILITIES

The Network has clearly defined the roles, core tasks and responsibilities of patients and health professionals and everyone is kept updated. Health professionals are aware of the different roles of individual patients and of patient representatives that represent a wider community when collaborating with them.

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AREAS OF COLLABORATION

01

Network strategy and management

Patients and health professionals discuss and agree on the priorities of the Network, including resource allocation

02

Healthcare

Development of care pathways, clinical practice guidelines, evidence reports, clinical consensus statements and other tools to support healthcare delivery and disease management

03

Education and training

Development of joint educational and training activities, bringing complementary knowledge and experience from clinicians and patients

04

Clinical research and registries

Good examples (e.g. the revision of Orphanet's rare diseases classification and the development of ERNs registries)

05

Information and outreach

Creation of education and informational resources, identifying knowledge gaps, outreach and awareness raising activities among the RD community and beyond.

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PATIENT-CLINICIAN COLLABORATIONS IN ERN CRANIO

- Video on genetics → collaboration with geneticists
- Research collaborations
- Communication materials on visible differences → collaboration with psychologists
- Guideline and consensus statement development → clinical & patient versions
- Patient-clinician engagement group
- National collaboration

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Example 1. Video on genetics

Goal: to inform patients and parents about the genetics underlying their condition.

Development of 3 videos:

1. Genetics & inheritance
2. Genetics in craniosynostosis
3. Genetic counseling

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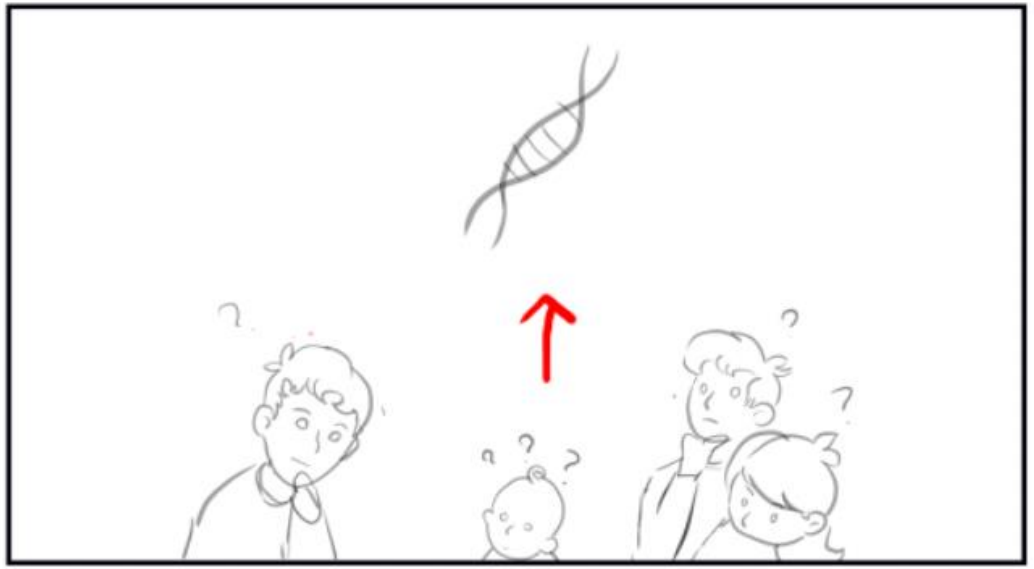
EXAMPLE 1. VIDEO ON GENETICS & INHERITANCE

Knowing the cause, may be important for you and your family members.

Family appears next to the baby thinking about the cause



Swipe up to DNA string

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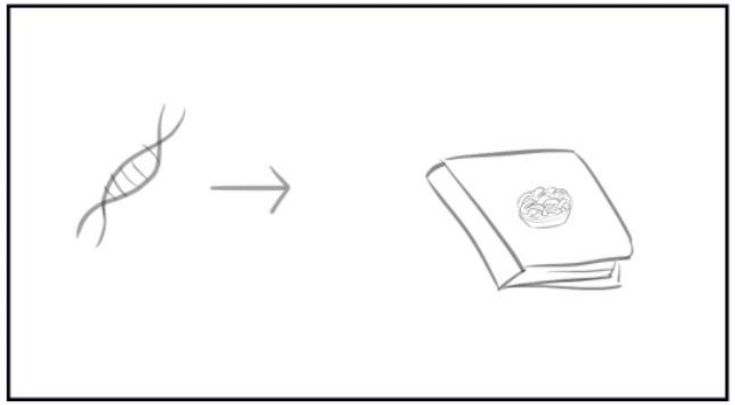
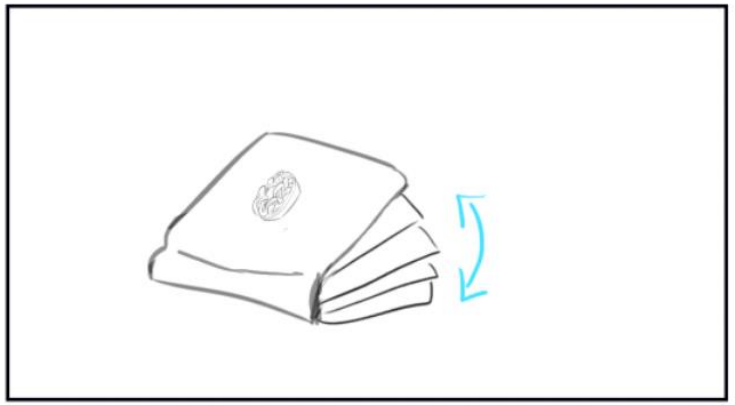
Draft storyboard of the first video:
GENETICS & INHERITANCE



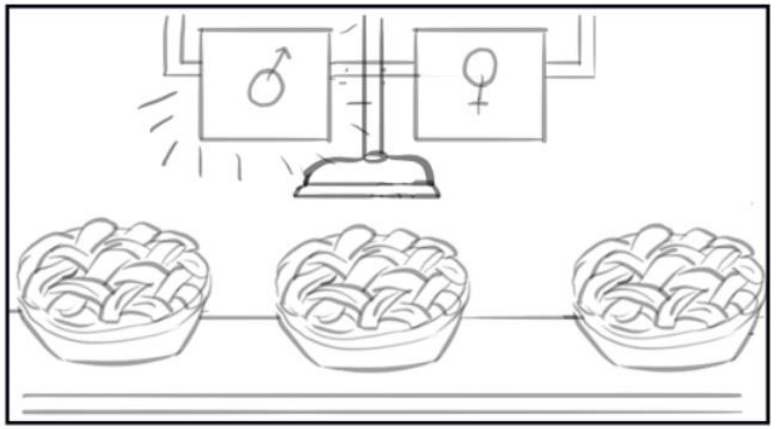
Imagine our genetic makeup as a personal cookbook.

DNA string transforms into a cookbook.



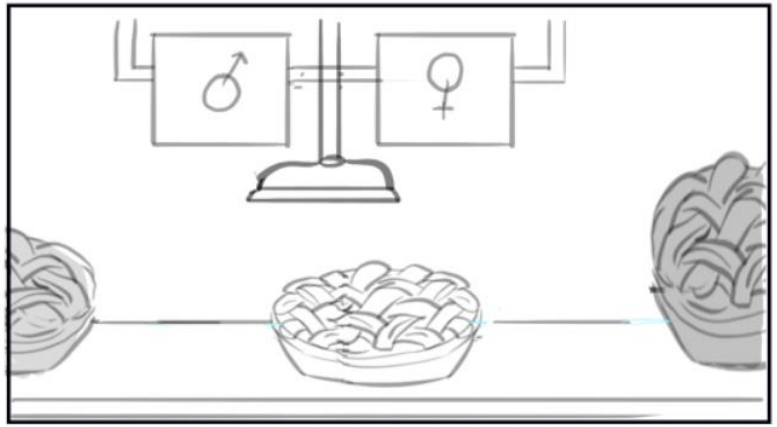
While genetics is a deeply intricate topic, think of each of us having our own unique apple pie recipe as an analogy to help clarify.

The book opens



Think of autosomal dominant inheritance as a dominant ingredient in the pie.If you inherit this specific ingredient from just one parent, it will significantly influence the pie's flavor.

We are in a factory were the pies are getting different flavours.
The signs of male or female also light up.



Each time this pie is baked, there's a 50% chance it'll have this distinct taste. Regardless of whether the pie is large or small, the flavor remains consistent.

Pies now have diffrent shapes and sizes but only 50%
of them have a diffrent taste.

A cookbook

&

apple pie

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Example 2. Research collaboration

Which patient to ask?

Table 2 Matching researchers questions and needs, and patients strengths and limitations: recommendations* and arguments

Researcher's question	Lived experience **Christine (see table 1)**	Personal story **William (see table 1)**	Collective perspective **Anouk (see table 1)**	Patient research Partner **Samira (see table 1)**
What is your personal experience of living with this disease?	+ May be too early	+ + Perfect match	+ Good match	- May know others who are better suited
What is your personal experience with the diagnosis?	+ + Recent unarticulated experience	+ + Recent, more articulated experience	- Personal experience with diagnosis may be outdated.	- - Personal experience with diagnosis will likely be outdated.
Can you read and understand the Patient Information Folder?	+ + Perfect match	+ Good match	- May be too knowledgeable, loss of the naïve patient experience. Could ask other patients.	- - Too knowledgeable, has learnt research language. Could ask other patients
Do you think other patients are willing to be included in my study (as participants)?	- Doesn't know other patients	- Doesn't know other patients	+ + Collective perspective: may not fully understand the study	+ + Collective perspective: may understand the study
Is my research question relevant for this patient group?	- - Doesn't know other patients (speaks to personal opinion only)	- - Doesn't know other patients (speaks to personal opinion only)	+ + Collective perspective	+ + Collective perspective May be aware of patients' research priorities
What are important outcomes that I should include in my study?	- - Doesn't know other patients	- - Doesn't know other patients	+ + Collective perspective	+ + Collective perspective May be aware of patient relevant outcomes
Can you comment on my research proposal?	- - Doesn't know other patients; not research ready.	- - Doesn't know other patients; not research ready.	+ Collective perspective, may not understand the proposal.	+ + Collective perspective, may understand the proposal.
Are you willing to be an equal member of the research team?	- - Doesn't know other patients; not research ready.	- - Doesn't know other patients; not research ready.	+ Collective perspective, not research ready; could join together with a more experienced patient.	+ + Collective perspective; research ready.
Could you act as a 'critical friend' and push back on the research team if necessary?	- - Grateful to be included; not sure of good/bad partnership yet; not research ready.	- - Grateful to be included; not sure of good/bad partnership yet; not research ready.	- Grateful to be included; not sure of good/bad partnership yet; not research ready.	+ + Understands more about being on a research team. Able to review critically and give constructive feedback. Ok to push back on research team

- - Strong recommendation not to engage.
- Weak recommendation not to engage.
+ Weak recommendation to engage.
++Strong recommendation to engage.
*Recommendations (starting points for discussion or interview, no strict directives).

Schoemaker et al. *Ann Rheum Dis.* 2023 Mar;82(3):312-315. doi: 10.1136/ard-2022-223561.

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EXAMPLE 2. RESEARCH COLLABORATION

		ROLE IN PROJECT/RESEARCH				
Phase	Activities	**Listener** Is given information	**Co-thinker** Is asked to give opinion	**Advisor** Gives (un) solicited advice	**Partner** Works as an equal partner	**Decision-maker** Takes initiative, (final) decision
Preparation	Support in writing of proposal by board member of LAPOSA		x			
	Defining outcome measures			x		
	Writing study information material for parents			x		
Execution	Interim analysis review on outcomes		x			
	Re-writing the chapter of the guideline				x	
Implementation	Re-writing the patient-version of the adapted guideline chapter				x	
	Adapting the courses for referring care providers			x		
	Adapting the LAPOSA patient-information					x

From project:
Comparing effectiveness of a conservative policy to craniofacial surgery in children with trigonocephaly

Erasmus Medical Center Rotterdam Netherlands

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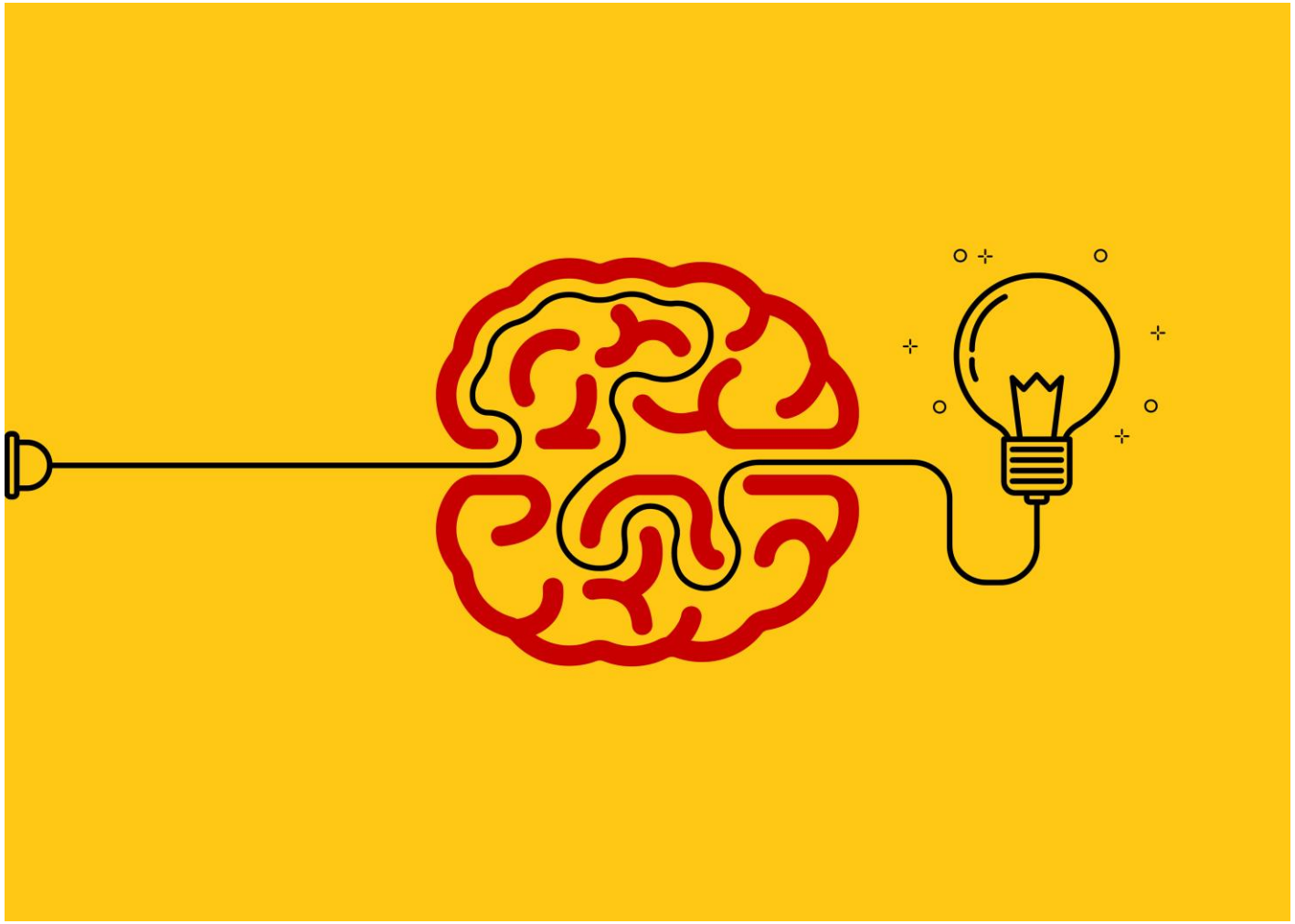
BRAINSTORM

Any ideas for collaboration?



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QUALITY OF LIFE ASSESSMENTS

Marizela Kljajić

Psychologist, PhD.

Gothenburg Craniofacial Unit

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What is Quality of Life?

- A multidimensional *construct* that considers physical, mental, and social components
- Describes well-being depending on number of factors

-duration and severity of illness?

-medication? Stressful events?

- Subjective concept

Why should we care about QoL?

- Treating a patient aims to improve QoL
- The QoL could be affected by the condition but could also be affected by the treatment itself
  - e.g. surgery is painful
- Unless life-saving, what is the indication for treatment?

How can we measure QoL?

- Questionnaires
- Generic and disease-specific
- Available for craniofacial conditions: FaceQ
- Psychometric properties (reliability,validity,norming?)

*In the past **ONE month** , how much of a **problem** has this been for you …*

About My Health and Activities *(problems with…)*	Ne	A	S	O	Al
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

About My Feelings *(problems with…)*	Ne	A	S	O	Al
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

How I Get Along with Others *(problems with…)*	Ne	A	S	O	Al
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

About School *(problems with…)*	Ne	A	S	O	Al
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

About Your Health

Thinking about the last week...

1.	Have you felt fit and well?	not at all	slightly	moderately	very	extremely
2.	Have you felt full of energy?	never	seldom	quite often	very often	always
3.	Have you felt sad?	never	seldom	quite often	very often	always
4.	Have you felt lonely?	never	seldom	quite often	very often	always
5.	Have you had enough time for yourself?	never	seldom	quite often	very often	always
6.	Have you been able to do the things that you want to do in your free time?	never	seldom	quite often	very often	always
7.	Have your parent(s) treated you fairly?	never	seldom	quite often	very often	always
8.	Have you had fun with your friends?	never	seldom	quite often	very often	always
9.	Have you got on well at school?	not at all	slightly	moderately	very	extremely
10.	Have you been able to pay attention?	never	seldom	quite often	very often	always

In general, how would you say your health is?

- excellent
- very good
- good
- fair
- poor

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KIDSCREEN-10 Index, Child and Adolescent Version

Figure 1 / UK (English) EQ-5D-5L Paper Self-Complete (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

SAMPLE

What information can measures give?

- What are they actually measuring?
- For how long is the assessment valid?
- Who is the respondent? Parent, mother or father, both? Child?

Important aspects to consider

- Is the questionnaire appropriate for your patients?
- Is it a valid questionnaire, do we know if it measures what we intend to measure?
- Does the questionnaire include self-report (pediatric)?
- Are we using it to help identify patients with needs or to evaluate the care that we provide?

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