RD Connect

The John Walton Muscular Dystrophy Research Centre

Newcastle University

Institute of Genetic Medicine

The Newcastle upon Tyne Hospitals NHS

NHS Foundation Trust

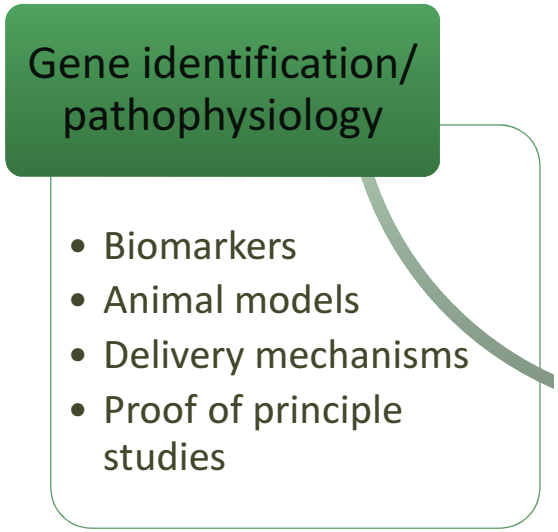
TRANSLATIONAL RESEARCH IN RARE AND NEUROMUSCULAR DISEASES - WHY DATA SHARING MATTERS

IRDiRC International Rare Diseases Research Consortium

Seventh Framework Programme

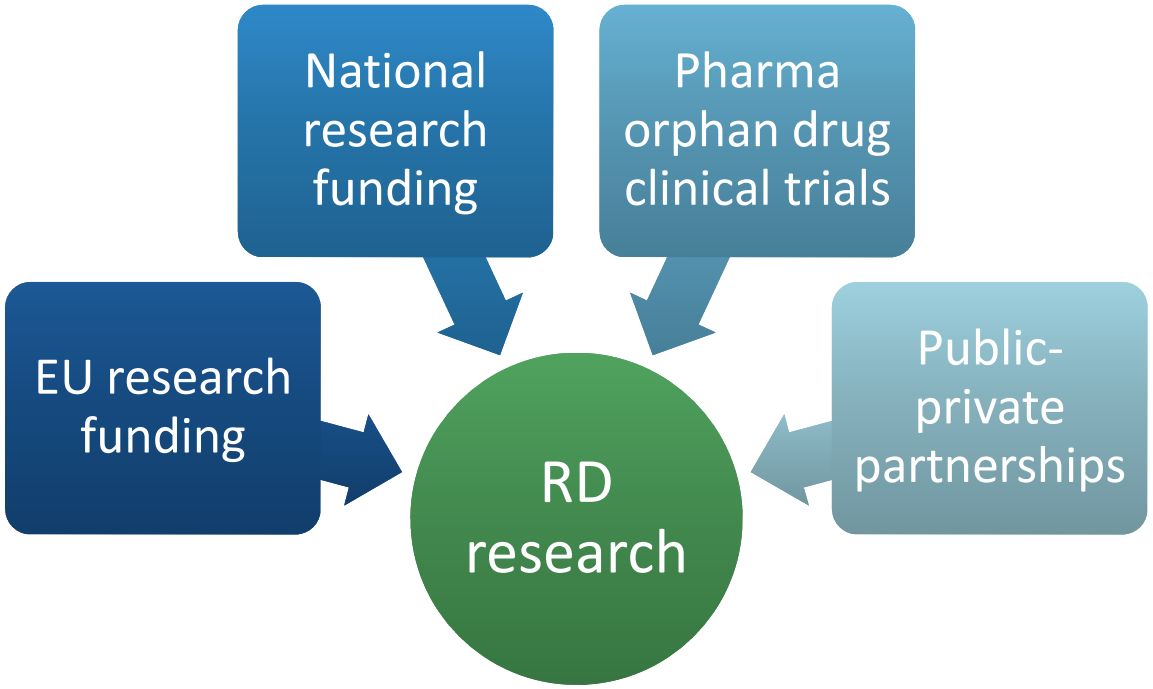
Hanns Lochmüller, Newcastle University

Addressing the translational pathway



Positive environment for RD research

- Recent years have seen an increased focus on RD research, with funding opportunities from different areas



Result: research projects multiply

TREAT-NMD
10M EUR "network of excellence" for rare inherited neuromuscular diseases

CARE-NMD
Implementing care standards for DMD across Europe, in particular Eastern Europe

Neuromics
12M EUR research project on nextgen omics approaches to neuromuscular and neurodegenerative disease

RD-Connect
12M EUR RD infrastructure: central global hub connecting registries, biobanks and clinical bioinformatics

NMD-Chip
High throughput sequencing (gene chips) for NMD diagnostics

MYO-SEQ
Exome sequencing of 1000 patients with limb girdle phenotype

RARE Bestpractices
Infrastructure for best practice sharing across rare diseases

EUCERD Joint Action for Rare Disease
Implementing RD policy and national plans across Europe

BIO-NMD
Identifying and validating pre-clinical biomarkers for diagnostics and therapeutics

SKIP-NMD
Clinical trial for morpholino antisense oligonucleotide exon skipping (53) in DMD

OPTIMISTIC
Natural history and exercise therapy clinical study in myotonic dystrophy

SCOPE-DMD
Clinical trial for 2O-ME antisense oligonucleotide exon skipping (45) in DMD

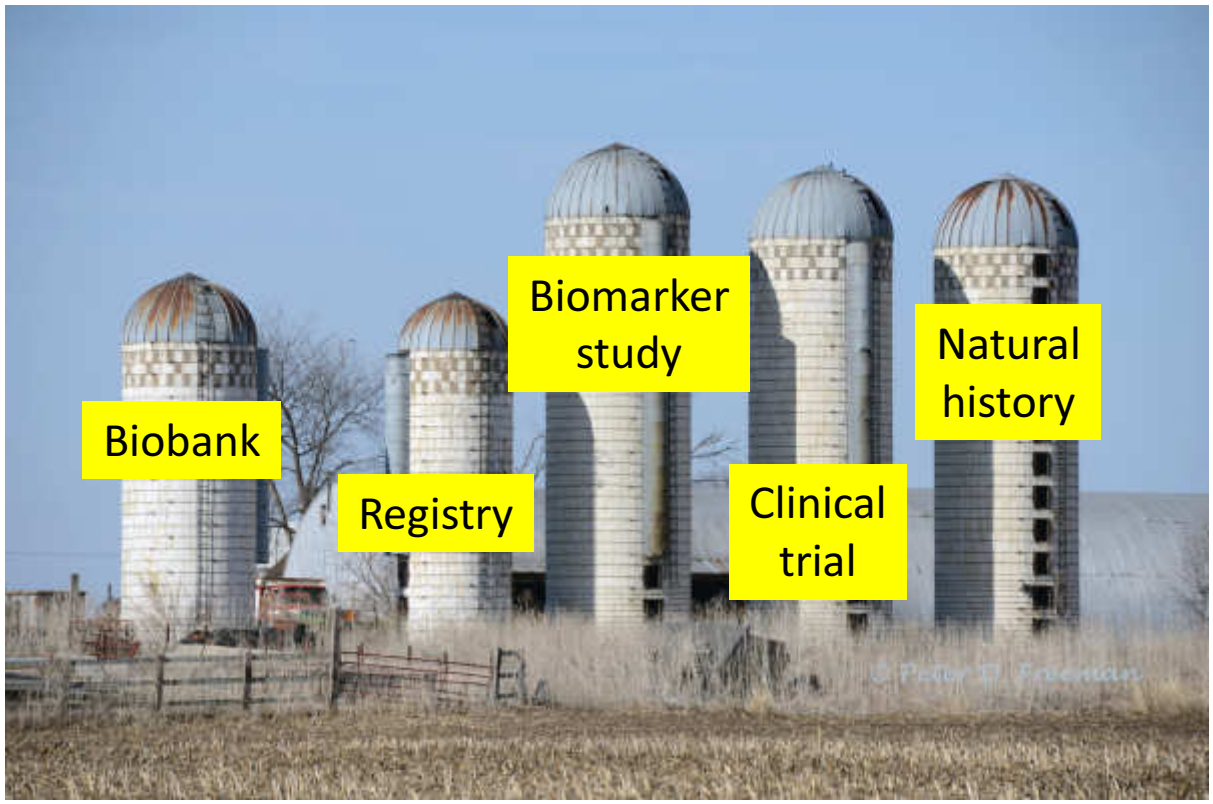
3Gb-TEST
Introducing diagnostic applications of '3Gb-Testing' in human genetics

BIOIMAGE-NMD
Development of imaging technologies for therapeutic interventions in rare diseases

MYO-MRI
Applications of MR imaging and spectroscopy techniques in neuromuscular disease

FUTURE …
Horizon 2020

But: risk of data silos increases



Sharing: What?

- Raw data from all types of studies
- Genomic data
- Phenotypic data
- Natural history data
- Clinical trial data
- Biosamples (blood, DNA, tissue samples, cell lines…)
- Linked data and samples
- Access to patients
- …

Sharing: Barriers

- **General**
  - Privacy protection issues: “do I have the patient’s permission?”
  - Lack of infrastructure: “I want to share data but where do I put it?”
  - Lack of standards and interoperability
- **Academia**
  - Culture of protecting research results: “someone else might scoop my publication!”
  - Lack of incentives for sharing
- **Industry**
  - IP issues/competition (sharing own data)
  - Concerns over data quality, regulatory compliance (reusing data from academia)

Sharing: Benefits

- Overcoming the “rare disease problem”
  - Cohort size
  - Powering trials
  - Finding confirmatory cases
- Reducing costs
- Reducing duplication of effort
- Facilitating validation of results
- Enabling engagement with experts and the patient community

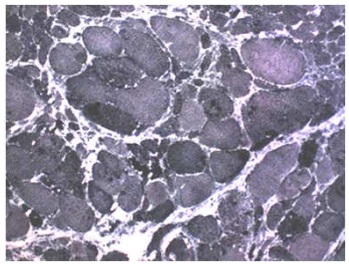
Using shared biosamples: Infrastructure – the MRC biobank

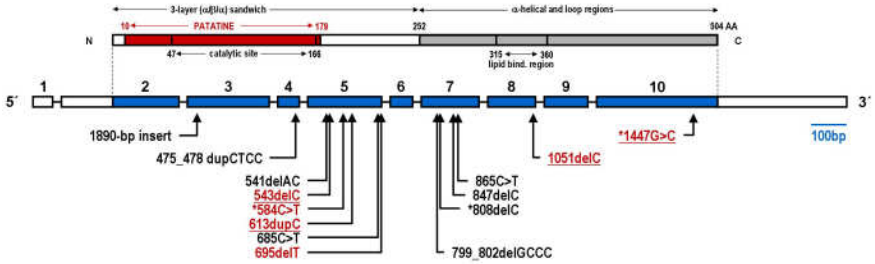
- MRC biobank established at 2 sites (Newcastle and London)
- Full member of EuroBioBank network and open catalogue
- More than 5000 NMD samples collected so far
- More than 100 different neuromuscular pathologies
- Samples distributed to more than 100 scientists (centre and external)
- More than 50 research publications acknowledging biobank
- Several successful grant proposals with strong biobank element

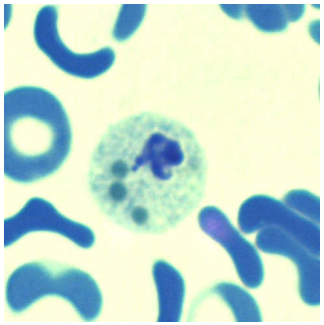
Using shared biosamples: Validating experimental therapies

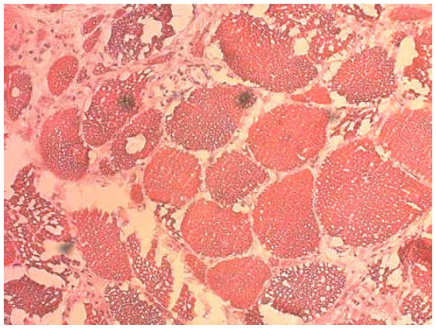
Using patient cells to validate experimental therapies:
Neutral Lipid Storage Myopathy due to PNPLA2 mutations

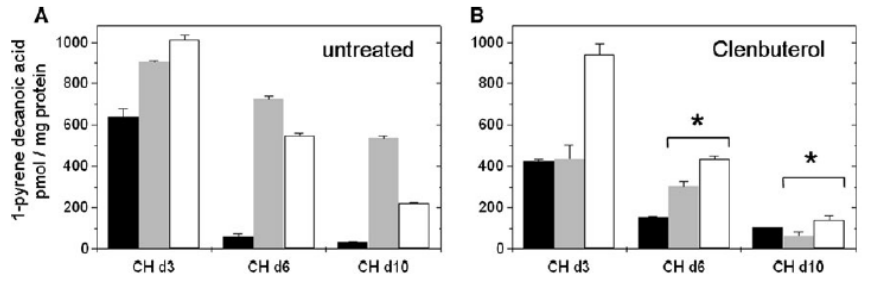
Recessive inheritance
Adult onset myopathy
Cardiomyopathy
Jordan bodies











Clenbuterol may be an attractive candidate for testing in animal models (R Horvath)

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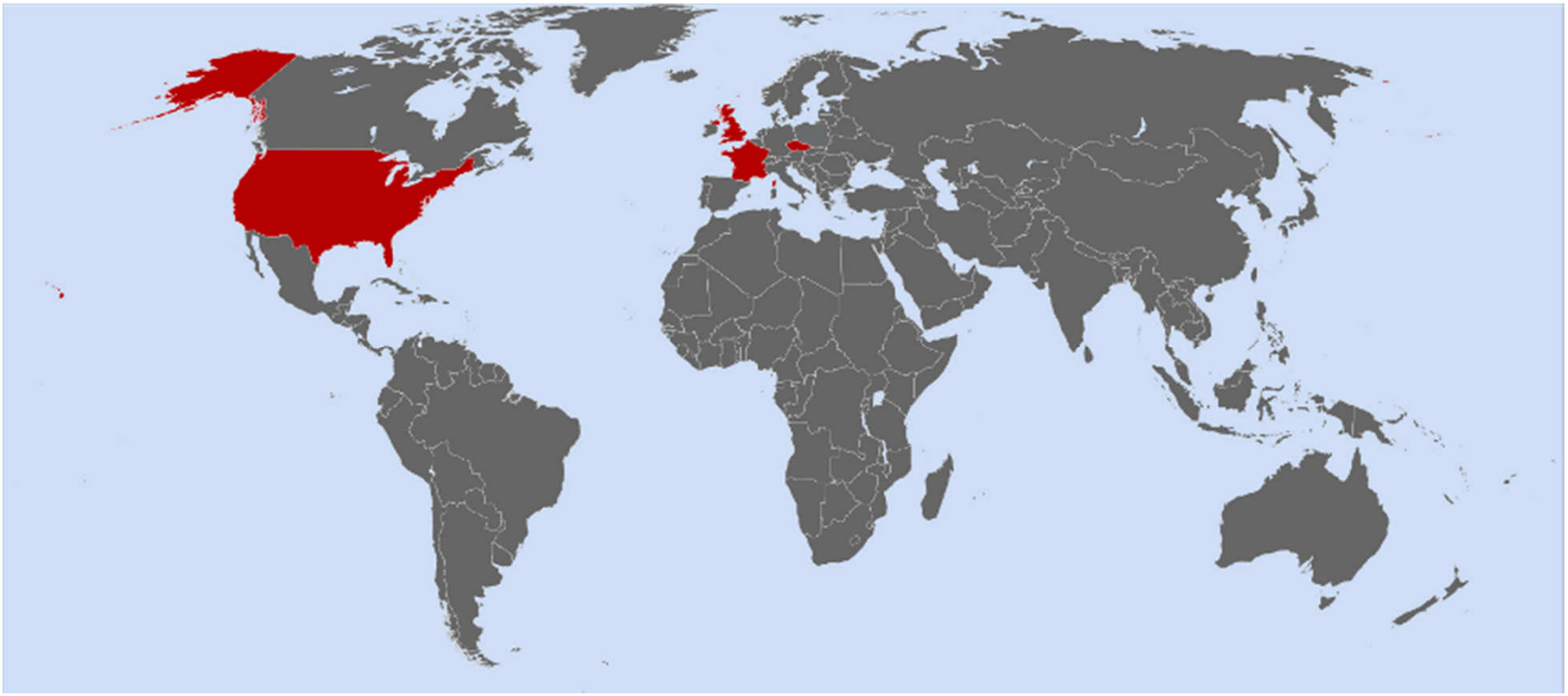
Sharing: example projects

TREAT-NMD
Neuromuscular Network

Patient registries:
DMD registries pre-TREAT-NMD (2007)



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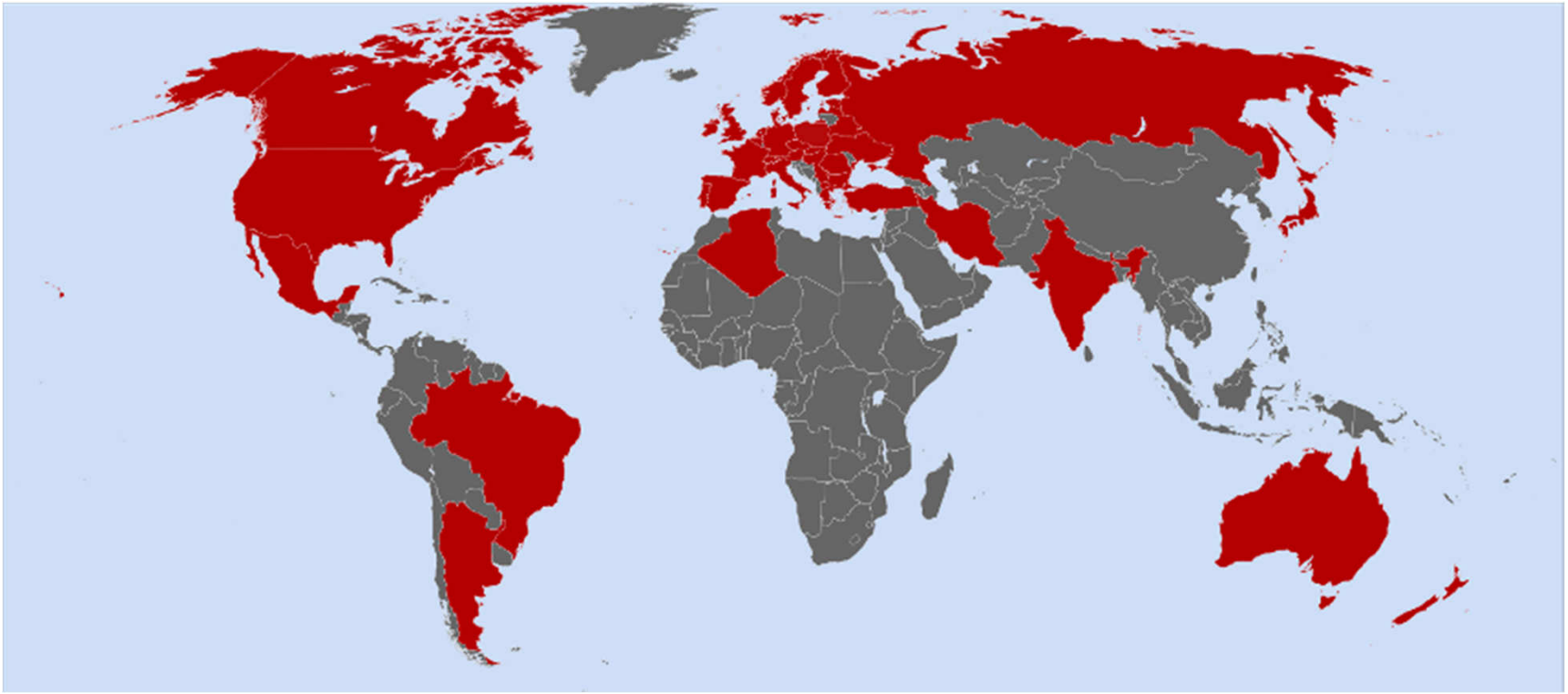
Patient registries:
DMD registries today (2015)



> 10,000 patients in 35+ countries – global data for multicentre trials

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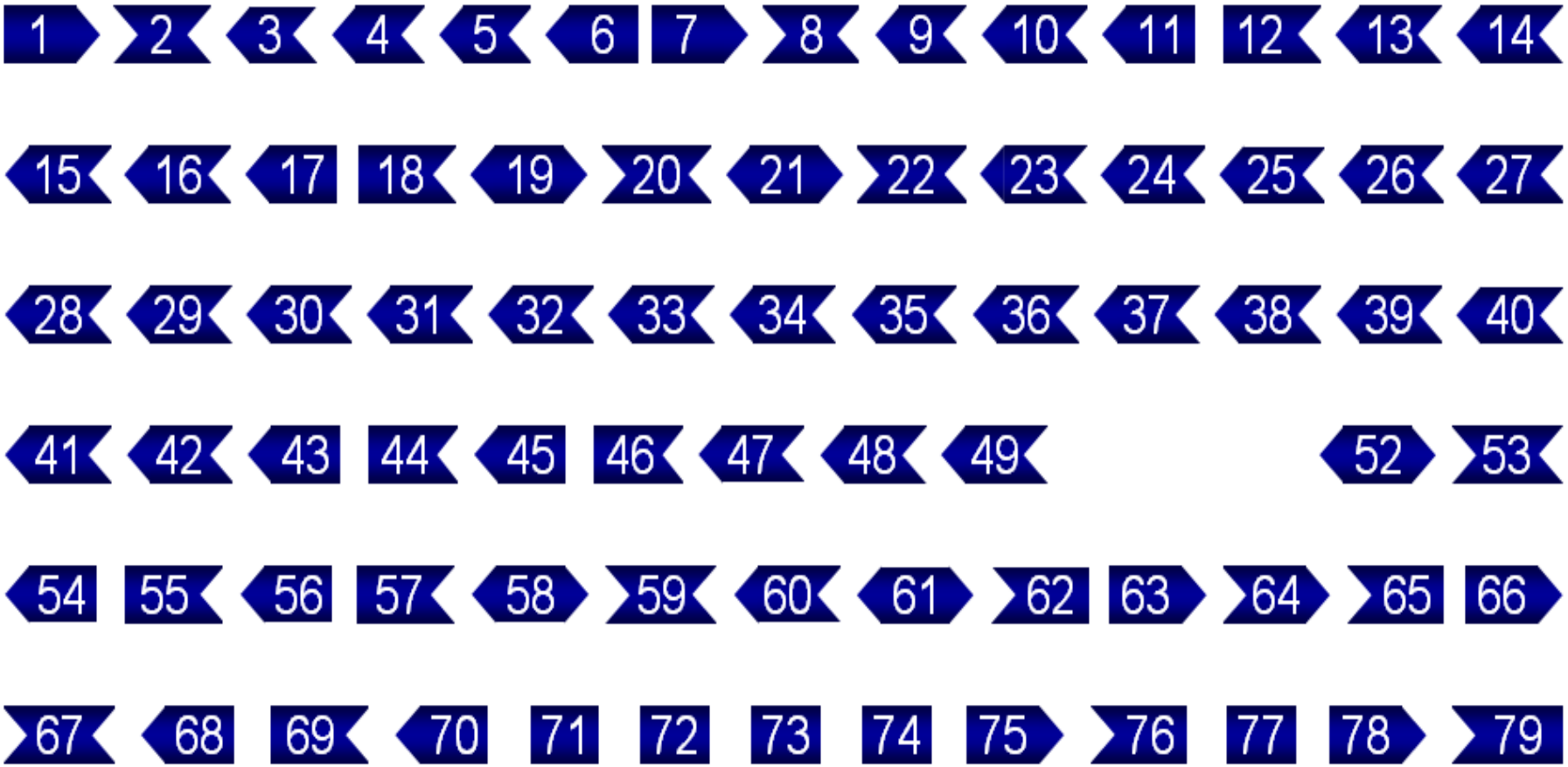
Patient registries as a tool for research

- Trial readiness (feasibility and recruitment)
- Standards of care – CARE-NMD
- Biomarker discovery and validation – BIO-NMD
- Burden of illness (health economics)
- Natural history

Exon skipping – gene and mutation specific therapy for Duchenne



DMD exon skipping – cumulative data from registries for trial feasibility

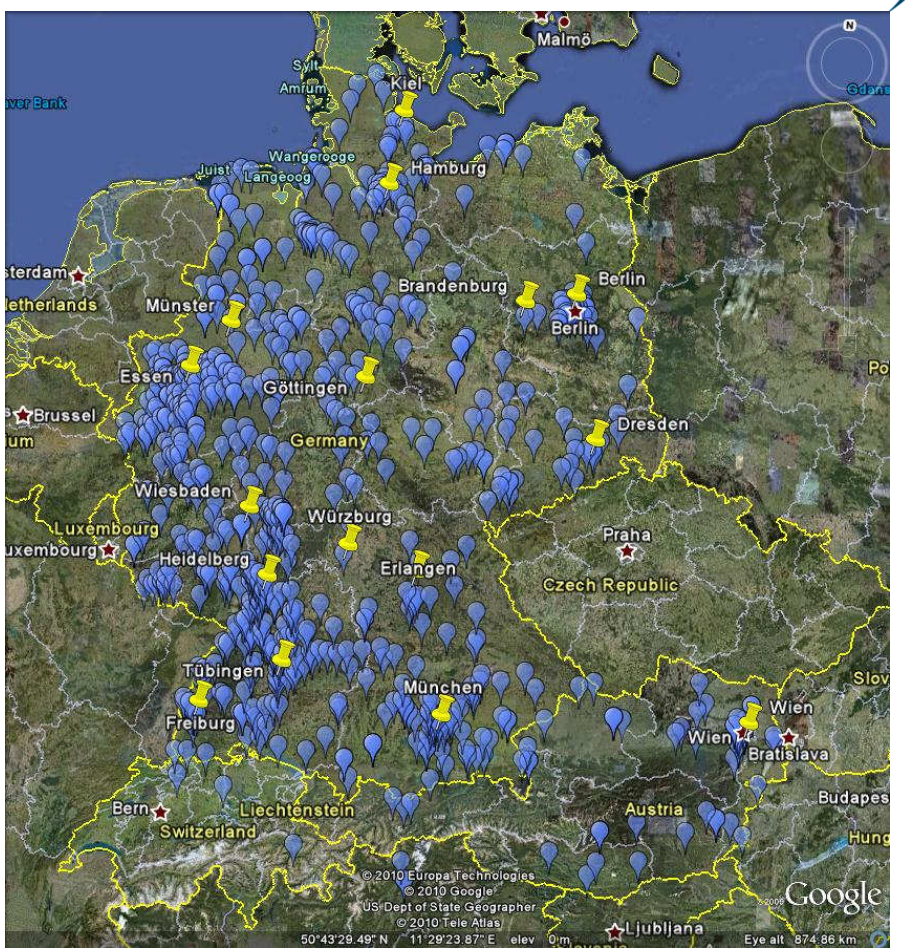
	Exon 44	Exon 45	Exon 50	Exon 51	Exon 53	all
Belgium	11	18	11	36	14	90
Bulgaria	2	3	0	2	2	9
Czech Republic and Slovakia	8	4	6	12	13	43
France	110	138	57	154	138	597
Germany	17	7	9	32	18	83
Hungary	0	2	0	8	2	12
Italy	7	7	9	10	12	45
Japan	55	37	20	74	64	250
Poland	24	72	12	60	61	229
Portugal	9	16	7	23	7	62
Spain	18	22	13	47	26	126
Switzerland	2	5	5	11	6	29
The Netherlands	11	1	4	7	9	32
Turkey	43	38	41	87	65	274
UK and Ireland	17	24	5	30	19	95
USA	65	91	36	119	99	410
all	399	485	235	712	555	2386

DMD exon skipping: trial feasibility and recruitment

Yellow pins:
German and Austrian
trial sites (16)

Blue pins:
DMD & BMD patients
in German/Austrian
patient registry (693)

May 2010



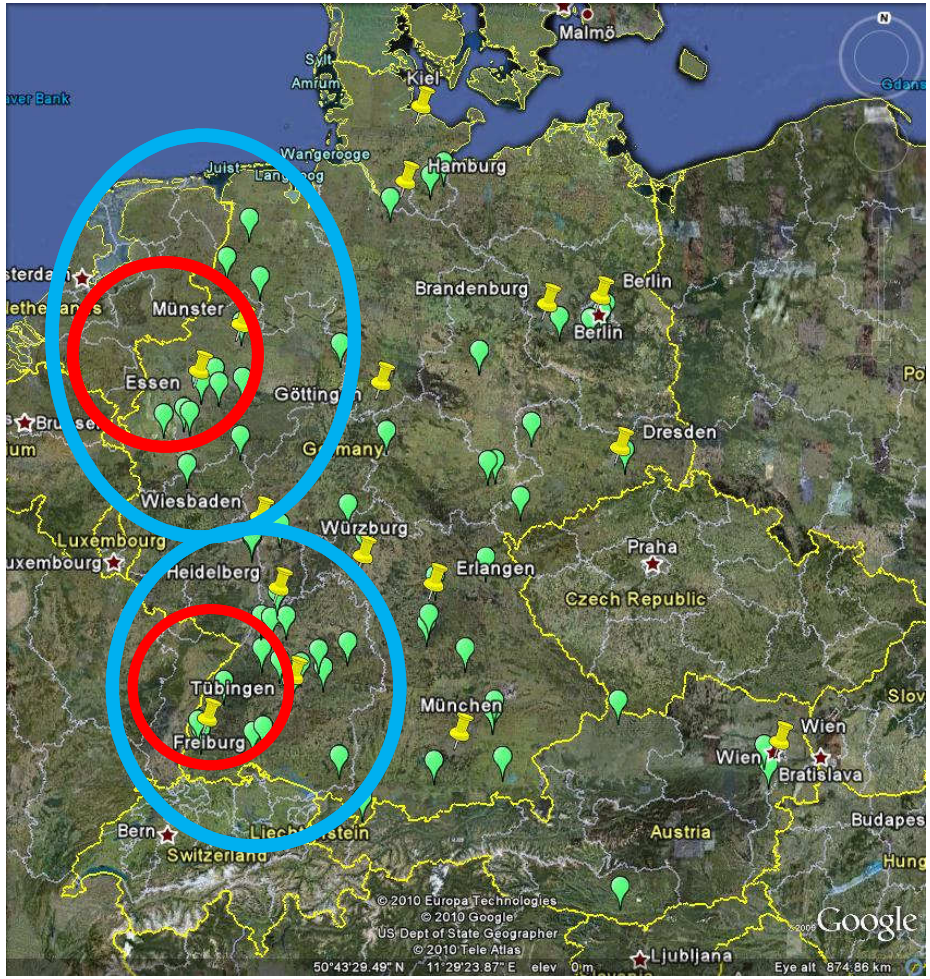
DMD exon skipping: trial feasibility and recruitment

Yellow pins:
German and Austrian trial sites

Green pins:
Patients meeting basic inclusion criteria for trial (67)

Red circle:
Under the care of Freiburg (4) and Essen (9)

Blue circle:
Recruitment potential (within 2 hours reach) Freiburg (15) and Essen (15)



Sharing: example projects: Infrastructure for RD data sharing

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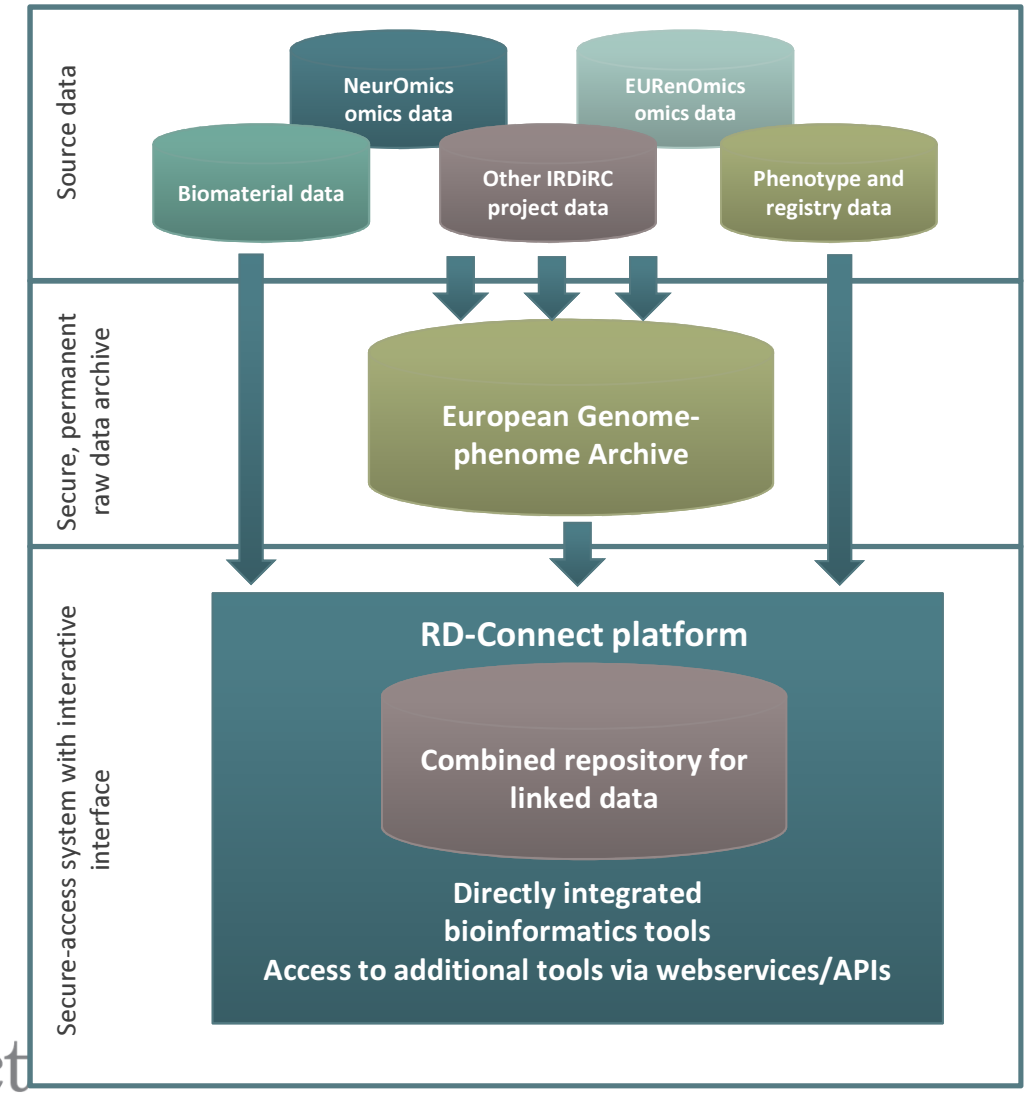
Infrastructure for RD data sharing RD-Connect

An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

Overarching objectives:

- Contribution to the IRDiRC objectives of delivering 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020
- Development of an integrated, quality-assured and comprehensive platform in which complete clinical profiles are combined with -omics data and sample availability for rare disease research, in particular IRDiRC-funded research.

Infrastructure for RD data sharing
Data flow within RD-Connect



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Some concluding thoughts

- Collaboration and data sharing are even more crucial in rare disease than common
- Opportunities arising from the increase in RD research will be missed if projects do not share data
- For large datasets (omics data), publications are not enough: raw data access is essential
- Number of projects (both academic and PPP) that have been made possible as a result of sharing are proof that hurdles can be overcome
- Requires a change in mindset on all sides
- Requires explicit policies and incentivisation
- Requires appropriate infrastructure

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