EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

MEDIZINISCHE
FAKULTÄT

Institut für
Medizinische Genetik und
Angewandte Genomik

State of the art

Diagnosing Genetic Diseases

Olaf Riess, MD
Institute of Medical Genetics and Applied Genomics, Tübingen, Germany

Genetic testing strategies

Main method in genetic diagnostics		50 years	10 years	2 years	„now“
		G-banded karyotype	**Microarray**	**Whole-exome sequence**	**Whole-genome sequence**
Appearance				CGGATGATTACCCGTT G.....GCTC TAGCTAGCTATA....	CGGATGATTACCCGTT GATATAGCTCTCGCTC GCTCTAGCTAGCTATA GGCTATGGGTGGGGGC
Resolution		5–10 Mb	50–100 kb	1 bp	1 bp
Number of loci probed		~500	~0.05–2 million	~50 million	3 billion
Variants detected		Variants >5 Mb	Copy number variants	Coding regions	Majority of variants
Variants per person	0 or 1	0 or 1	10–100s	~20,000	4–5 million
Diagnostic yield	Low	→	→	→	High
Incidental findings	Low	→	→	→	High

Modified from Wright/FitzPatrick/Firth Nat Rev Genet 2018

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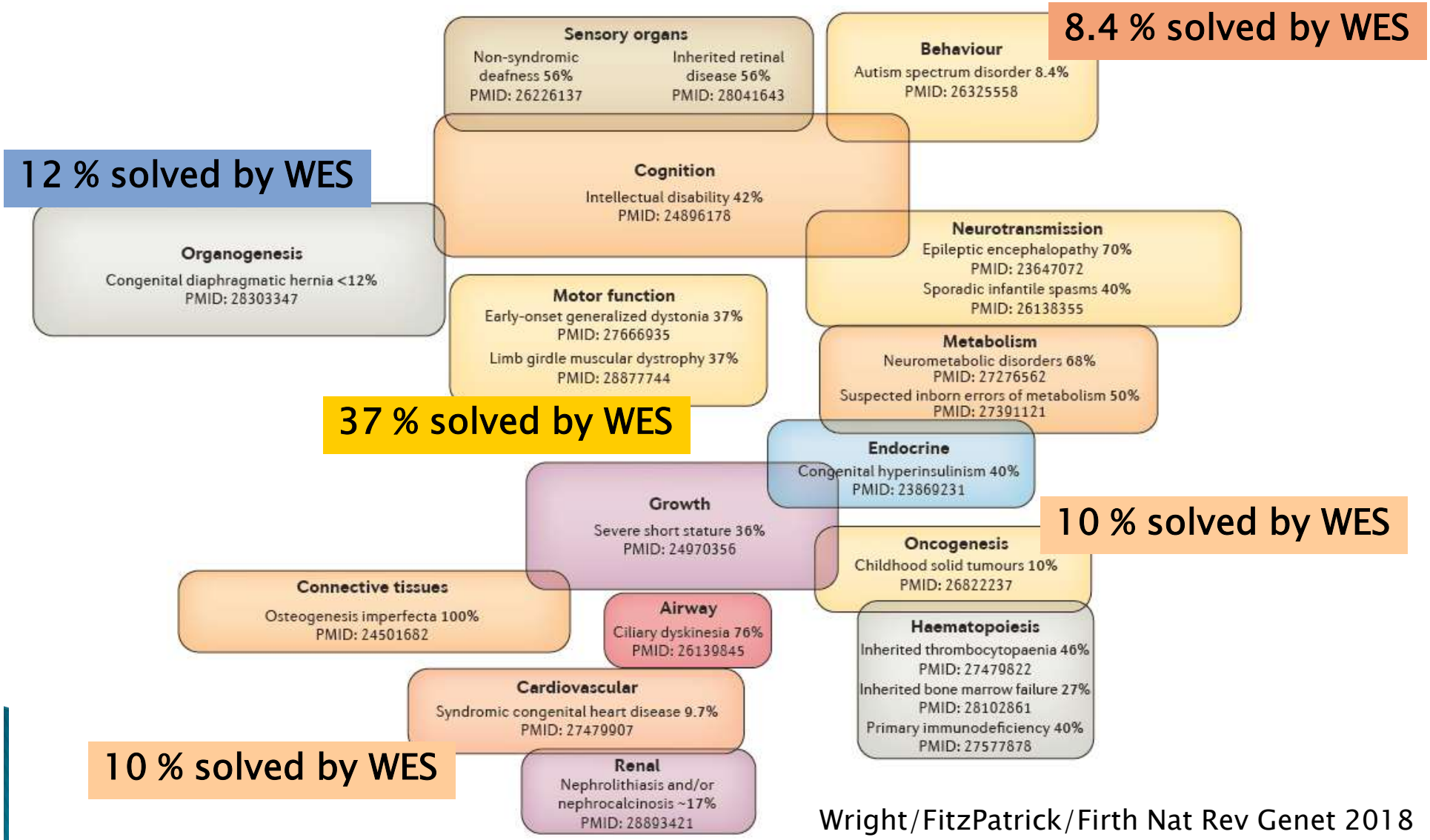
Zentrum für Seltene Erkrankungen

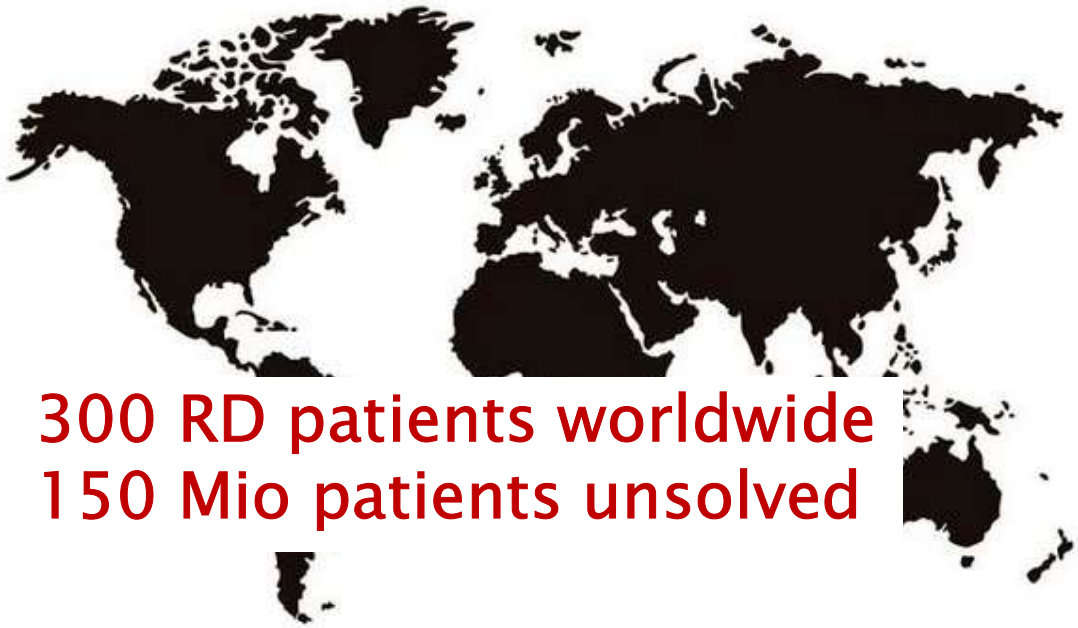
Why do we need to implement Whole Genome Analysis (WGS) in diagnostics?

Diagnostic sensitivity of todays WES in pediatric diseases



Wright/FitzPatrick/Firth Nat Rev Genet 2018

UNSOLVED after WES:
50% of all patients with a rare disease will not have access to health care without having a clear diagnosis



300 RD patients worldwide
150 Mio patients unsolved

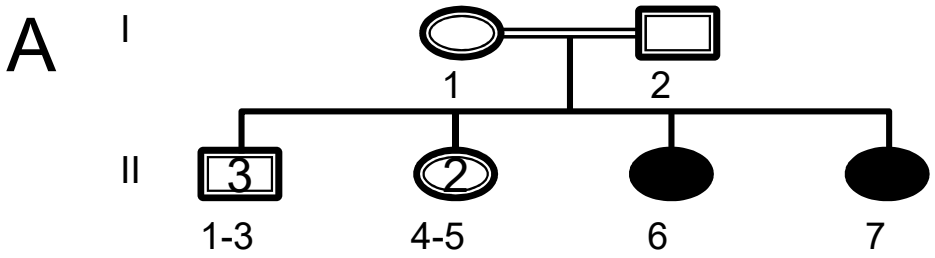
30 Mio patients in Europe
15 Mio unsolved

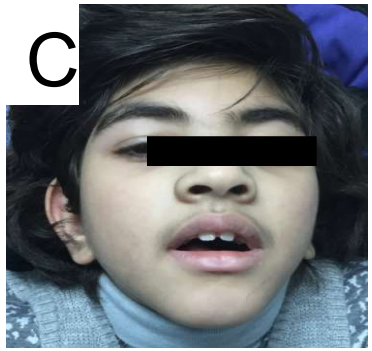
3-4Mio RD patients in Germany
1.5 Mio unsolved after WES

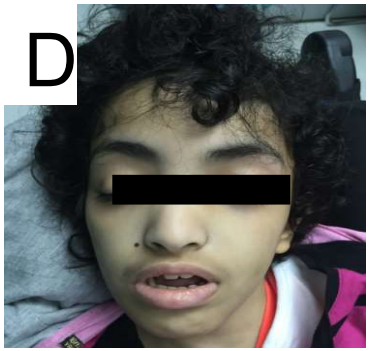
How can we increase diagnostic sensitivity?

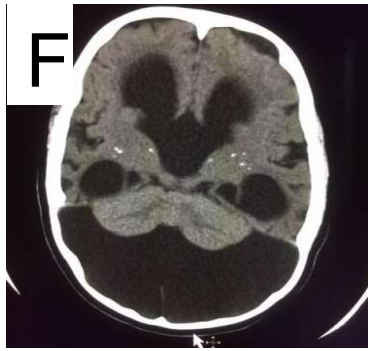
Defining new disease genes

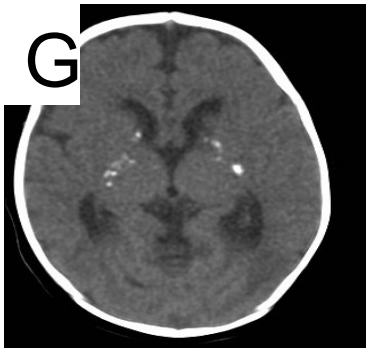
Defining new disease mechanisms





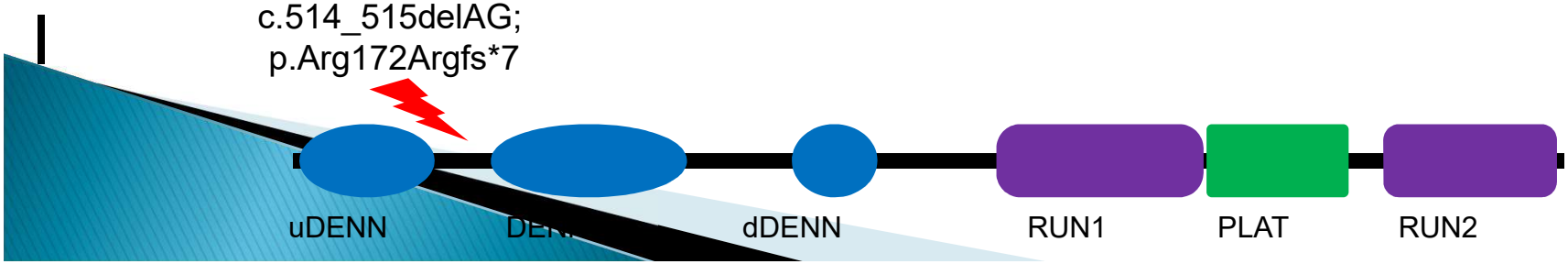






Family I: II-6

Family I:
II-7



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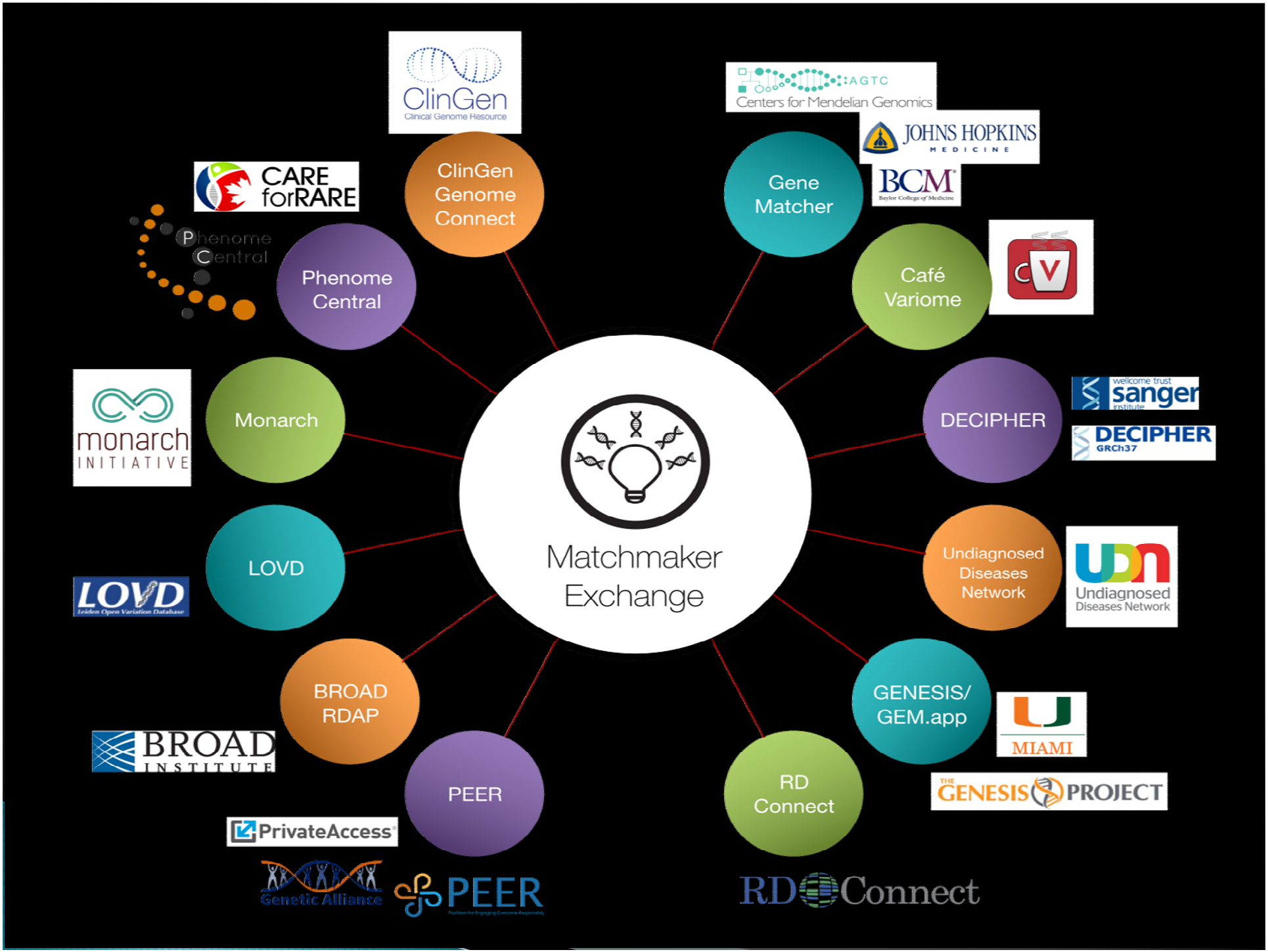
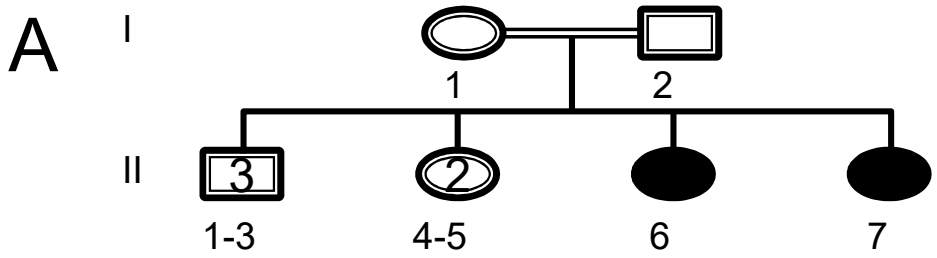
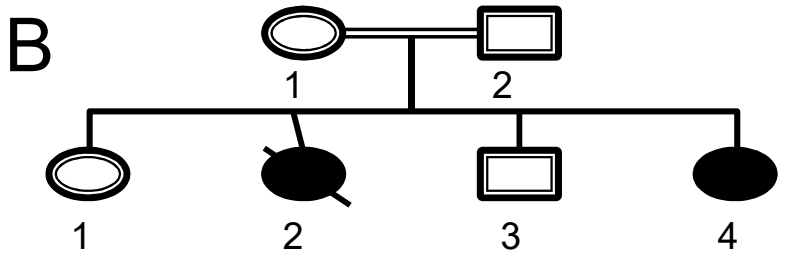
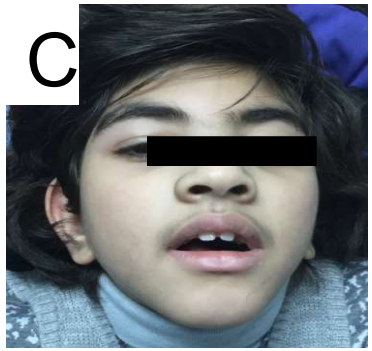
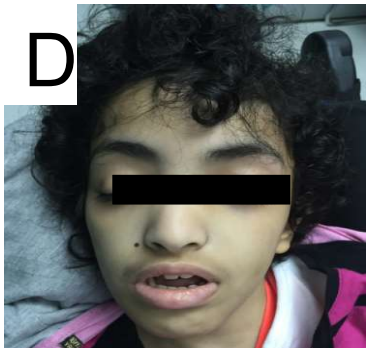
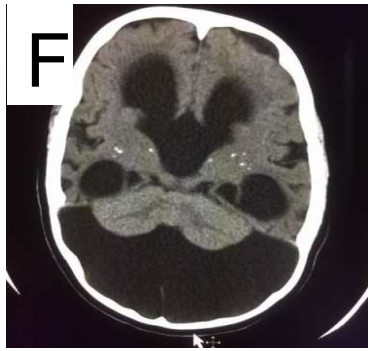

ClinGen
Clinical Genome Resource
ClinGen Genome Connect
CARE forRARE
Phenome Central
Phenome Central
monarch INITIATIVE
Monarch
LOVD
Leiden Open Variation Database
LOVD
BROAD INSTITUTE
BROAD RDAP
PrivateAccess
Genetic Alliance
PEER
PEER
Matchmaker Exchange
AGTC
Centers for Mendelian Genomics
JOHNS HOPKINS MEDICINE
BCM
Baylor College of Medicine
Gene Matcher
Café Variome
DECIPHER
welcome trust sanger institute
DECIPHER GRCh37
Undiagnosed Diseases Network
Undiagnosed Diseases Network
GENESIS/ GEM.app
MIAMI
THE GENESIS PROJECT
RD Connect
RD Connect

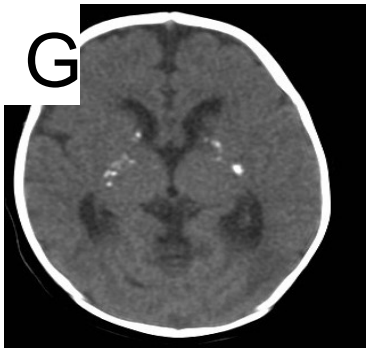












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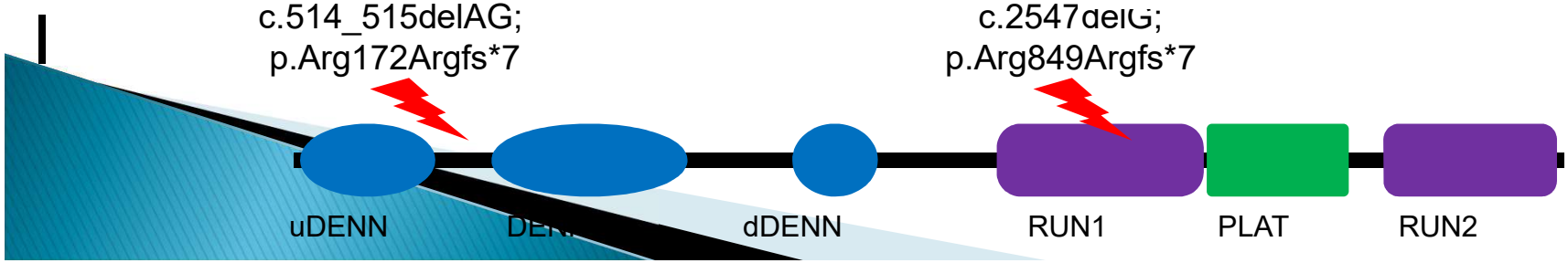

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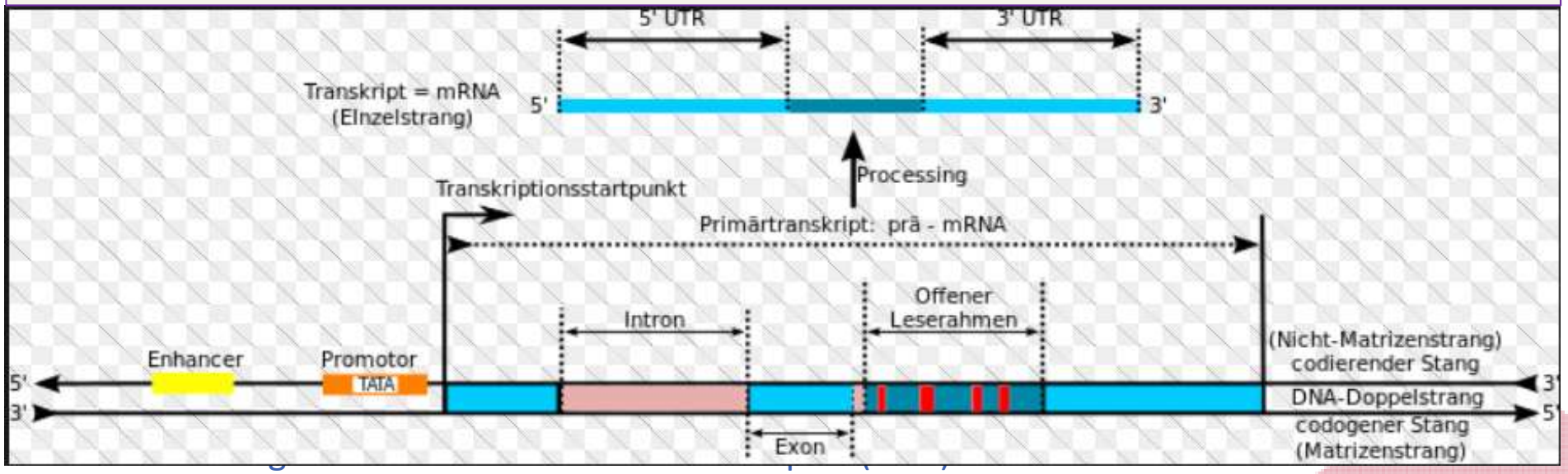
Hurdle of sensitivity in diagnostics

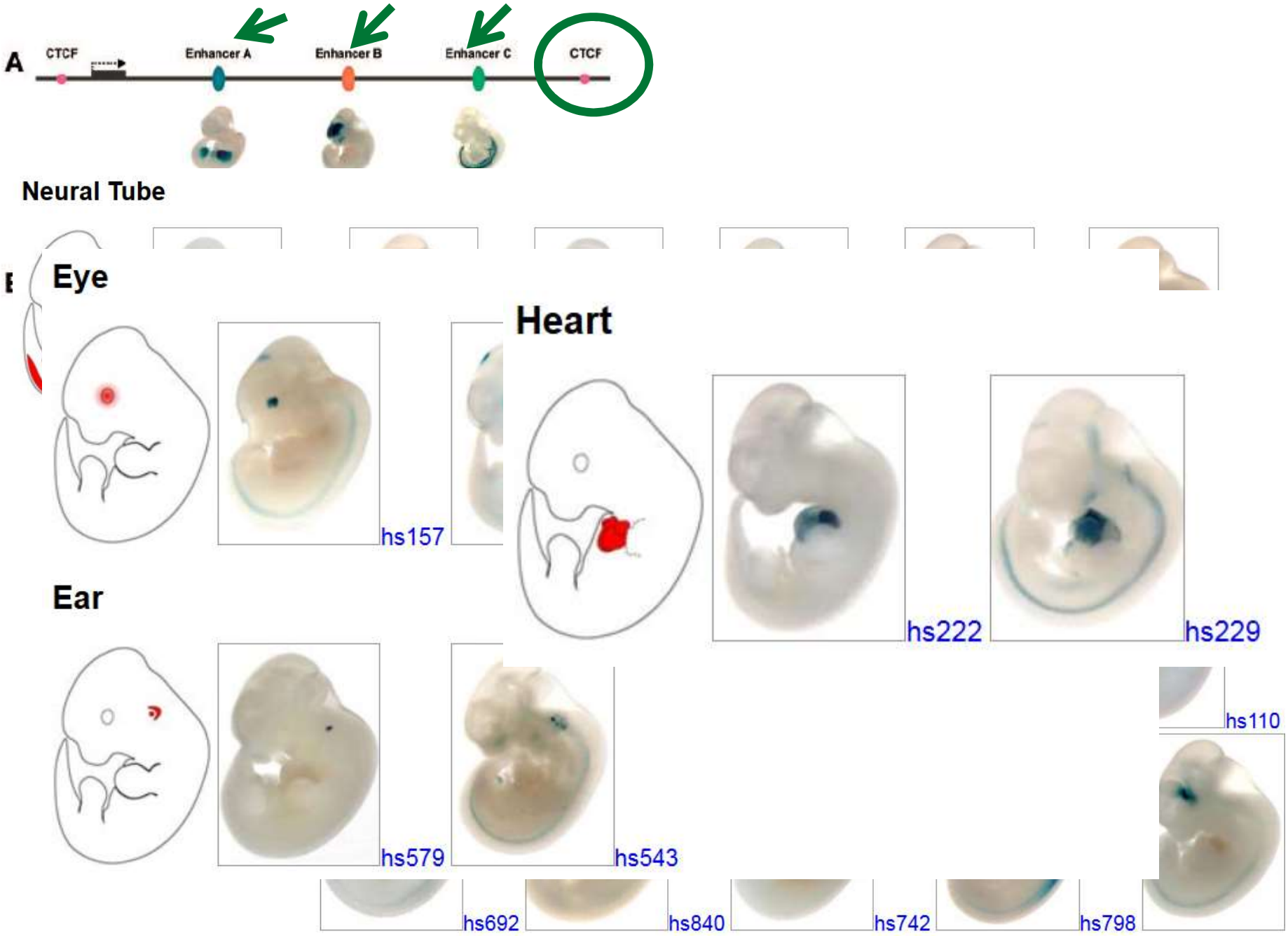
Neuromics: Statistics on WES/WGS

WES 5% **WGS**

The exome is only 1-2% of our entire genome!

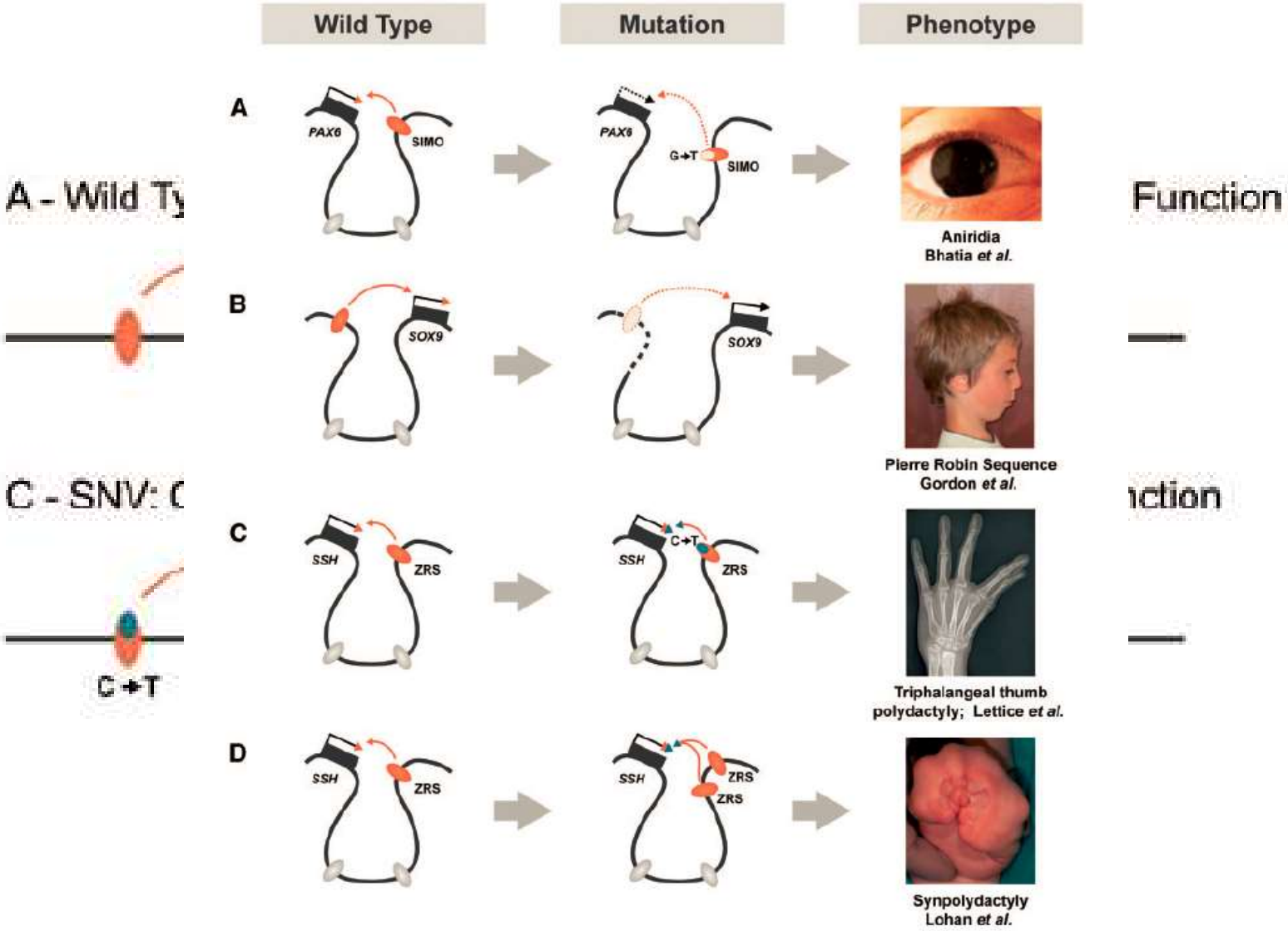


NeuroOmics



https://enhancer.lbl.gov/gallery_n.html

Effects of mutations
in non-coding regions altering gene expression

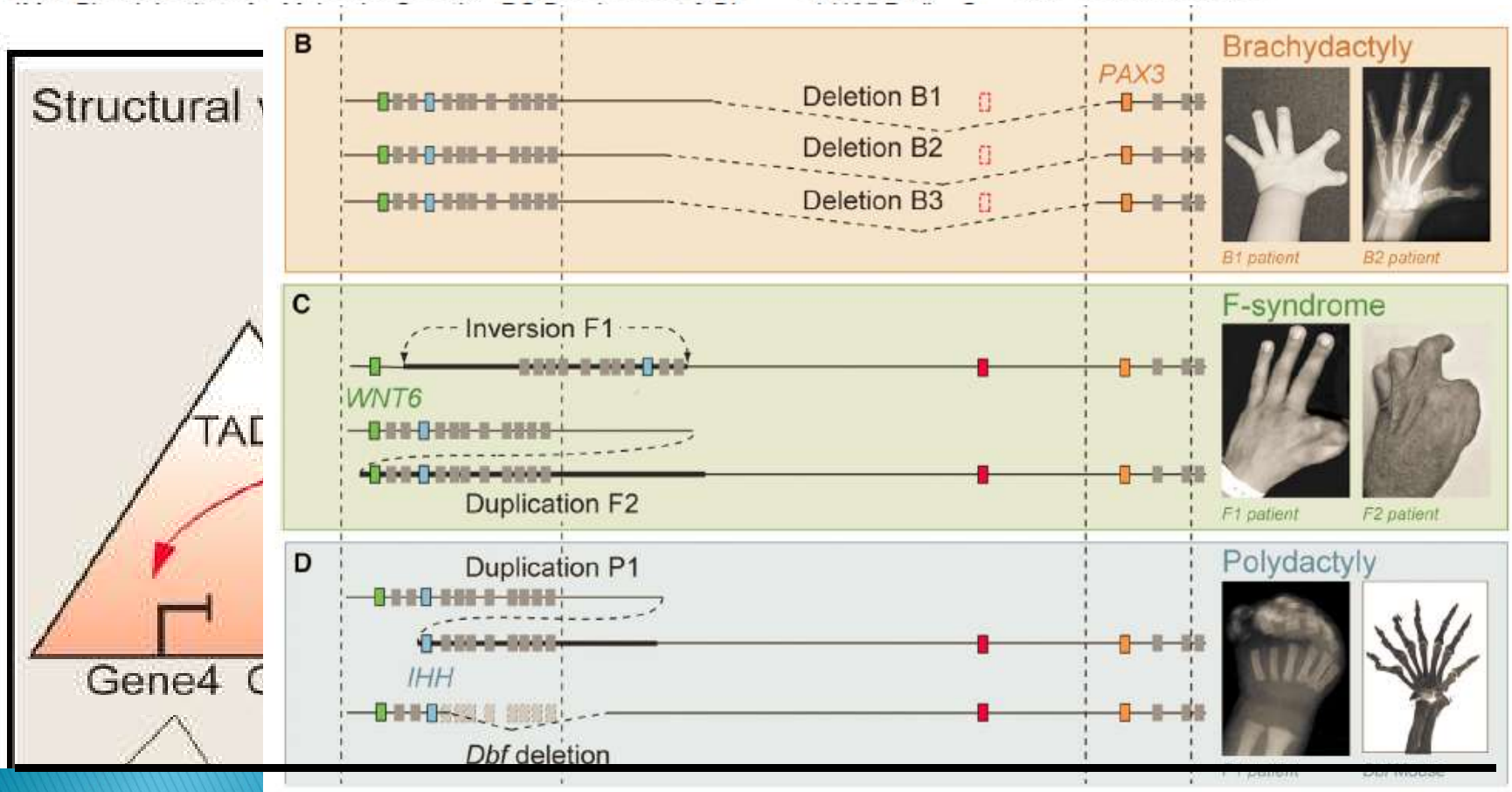


Cell

Article

Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions

Darío G. Lupiáñez,[1,2] Katerina Kraft,[1,2] Verena Heinrich,[2] Peter Krawitz,[1,2] Francesco Brancati,[3] Eva Klopocki,[4] Denise Horn,[2] Hülya Kayserili,[5] John M. Opitz,[6] Renata Laxova,[6] Fernando Santos-Simarro,[7,8] Brigitte Gilbert-Dussardier,[9] Lars Wittler,[10] Marina Borschiwer,[1] Stefan A. Haas,[11] Marco Osterwalder,[12] Martin Franke,[1,2] Bernd Timmermann,[13] Jochen Hecht,[1,14] Malte Spielmann,[1,2,14] Axel Visel,[12,15,16] and Stefan Mundlos[1,2,14,*]



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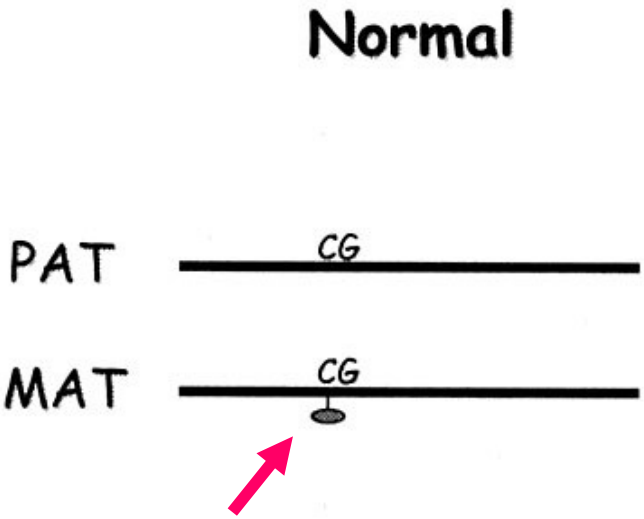
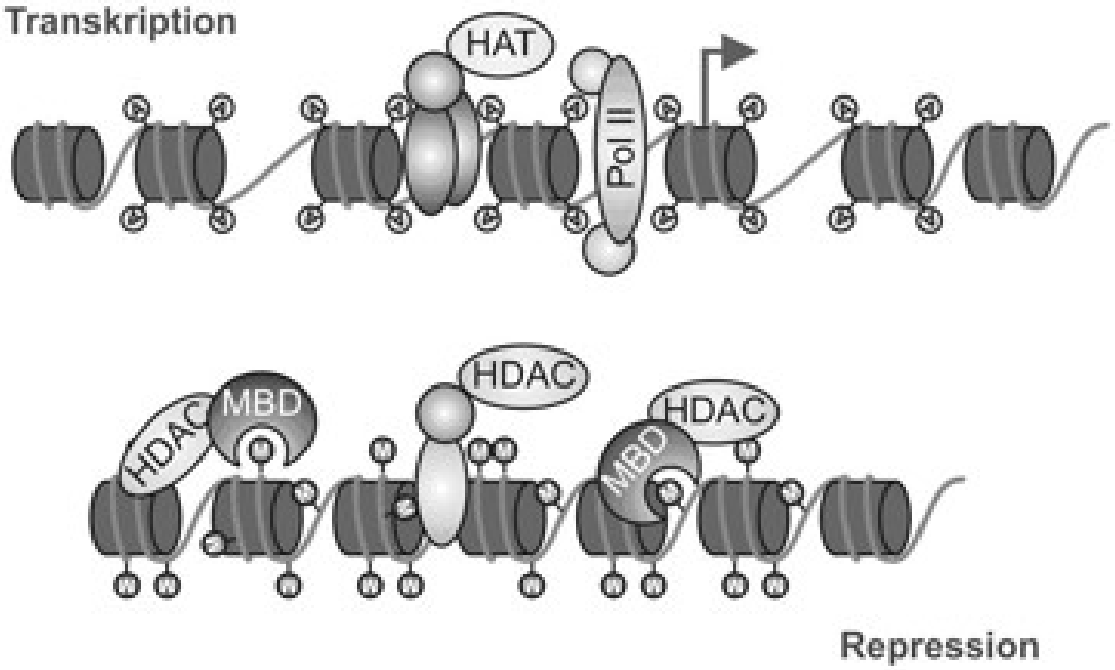
Medizinische Genetik und
Angewandte Genomik

DNA – Methylation



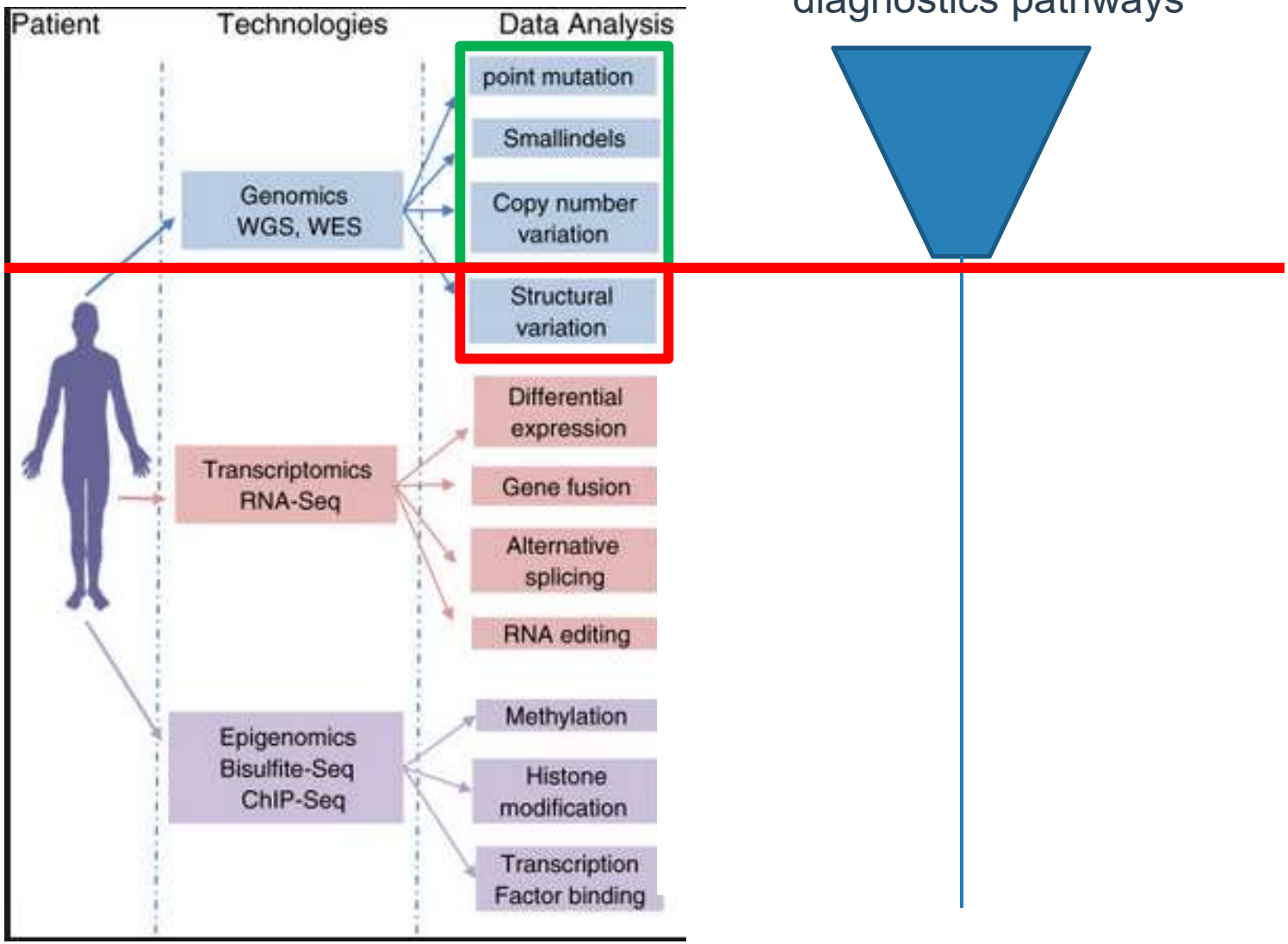
„Genomic Imprinting“



Colin Farrell‘s son has Angelman syndrome

COLIN FARRELL is thankful his young son JAMES was diagnosed with neuro-genetic disorder Angelman Syndrome early - because it ended weeks of torment for the actor. The In Bruges star reveals the four-year-old started showing signs of illness just before his first birthday, prompting the Irishman and his former partner, Kim Bordenave, to seek help. In a candid interview on Irish TV show Tubridy Tonight, the actor says, "I've been very lucky that it was early because he started having seizures at about eight or nine months... We got (an) early intervention." Farrell reveals doctors initially thought his son had cerebral palsy, but the correct diagnosis was fast - and a relief. The actor adds, "Angelman's is a neuro-genetic disorder. The 15th chromosome is dormant. It affects their fine motor skills. They say that one in 30,000 children is affected by it." But the actor refuses to feel sorry for himself or his "little fella": "He's nothing but a gift. As far as I'm concerned, he's exactly the way he should be... He has his own path. He's just brilliant." Farrell admits he felt terrible when he went public with his son's disorder last year (07) after people started asking questions about the actor's involvement with the Special Olympics. He adds, "I felt like I was betraying him, like it could be misconstrued as shame, which would be terrible, because he's such a celebration."

Technical hurdles in diagnostics



Modified from Shyr and Liu 2013

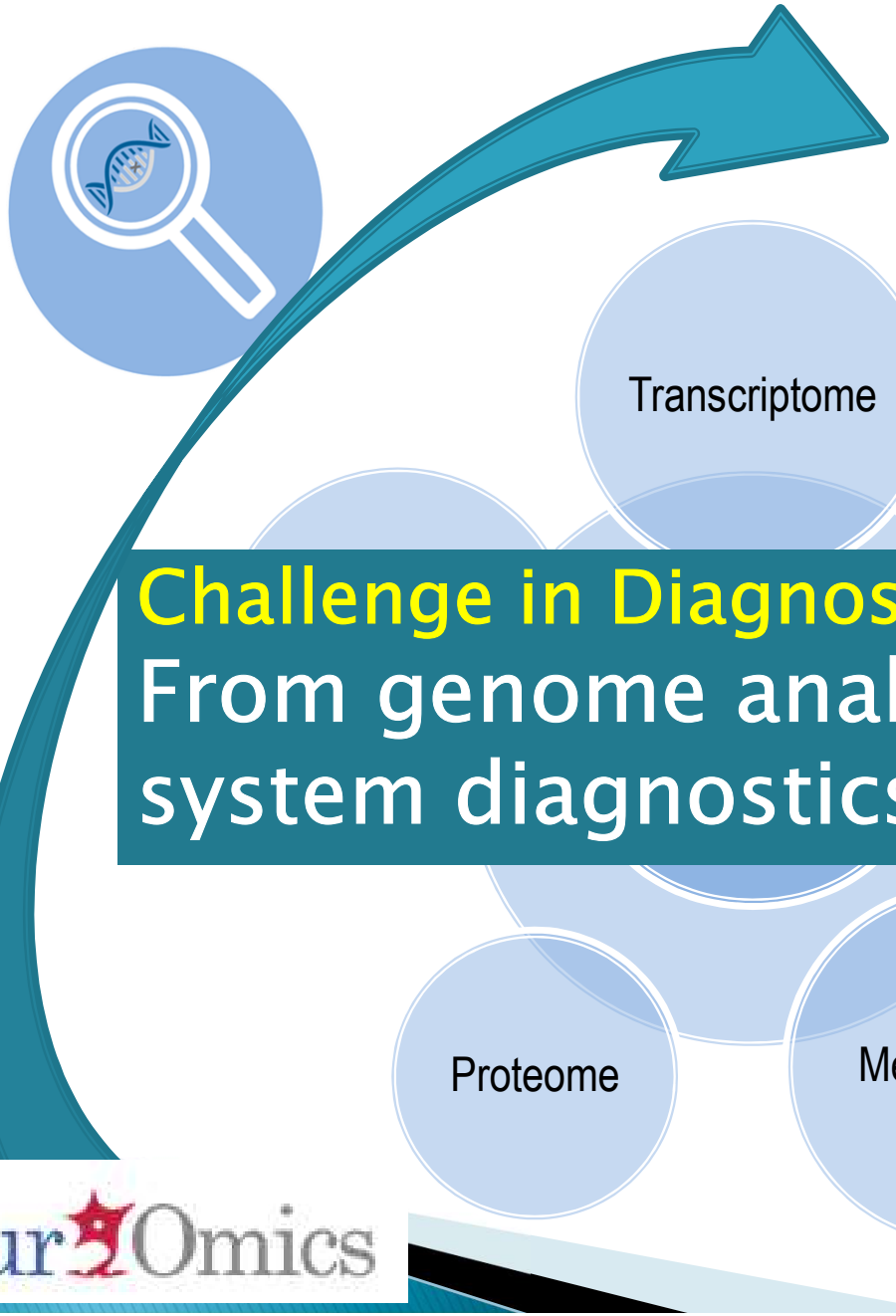
Multi-platform discovery of haplotype-resolved structural variation in human genomes

Mark J.P. Chaisson[1,2*], Ashley D. Sanders[3*], Xuefang Zhao[4,5*], Ankit Malhotra[6]†, David Porubsky[7,8]†, Tobias Rausch[3]†, Eugene J. Gardner[9]†, Oscar Rodriguez[10]†, Li Guo[11]†, Ryan L. Collins[5,12]†, Xian Fan[13]†, Jia Wen[14]†, Robert E. Handsaker[15]†, Susan Fairley[16]†, Zev N. Kronenberg[1]†, Xiangmeng Kong[17]†, Fereydoun Hormozdiari[18,19]†, Dillon Lee[20]†, Aaron M. Wenger[21]†, Alex Hastie[22]†, Danny Antaki[23]†, Peter Audano[1], Harrison Brand[5], Stuart Cantsilieris[1], Han Cao[22],Eliza Cerveira[6], Chong Chen[13], Xintong Chen[9], Chen-Shan Chin[21], Zechen Chong[13], Nelson T. Chuang[9], Deanna M. Church[25], Laura Clarke[16], Andrew Farrell[20], Joey Flores[26], Timur Galeev[17], David Gorkin[34, 35], Madhusudan Gujral[23], Victor Guryev[7], William Haynes Heaton[25], Jonas Korlach[21], Sushant Kumar[17], Jee Young Kwon[6], Jong Eun Lee[27], Joyce Lee[22], Wan-Ping Lee[6], Sau Peng Lee[30], Patrick Marks[25], Karine Viaud-Martinez[26], Sascha Meiers[3], Katherine M. Munson[1], Fabio Navarro[17], Bradley J. Nelson[1], Conor Nodzak[14], Amina Noor[23], Sofia Kyriazopoulou-Panagiotopoulou[25], Andy Pang[25], Yunjiang Qiu[24, 27], Gabriel Rosanio[23], Mallory Ryan[6], Adrian Stütz[3], Diana C.J. Spierings[7], Alistair Ward[20], AnneMarie E. Welch[1], Ming Xiao[31], Wei Xu[25],Chengsheng Zhang[6], Qihui Zhu[6], Xiangqun Zheng-Bradley[16],Goo Jun[32]Δ, Li Ding[33]Δ, Chong Lek Koh[29]Δ, Bing Ren[34, 35]Δ, Paul Flicek[16]§Δ, Ken Chen[13]§Δ, Mark B. Gerstein[35,36]§Δ, Pui-Yan Kwok[37] §Δ, Peter M. Lansdorp[7,38,39]§Δ, Gabor Marth[20]§Δ, Jonathan Sebat[23,28,34]§Δ, Xinghua Shi[14]§Δ, Ali Bashir[10]§Δ, Kai Ye[13]§Δ, Scott E. Devine[9]§Δ, Michael Talkowski[5, 41,42,43,44]§Δ, Ryan E. Mills[4,45]§Δ,Tobias Marschall[8]§Δ, Jan Korbel[3,18]‡§Δ, Evan E. Eichler[1,46]‡§Δ, Charles Lee[6,47]§‡Δ

2018

- Short and long read NGS, and strand specific
- 3 Trios
- 818,181 In/Dels per genome <50bp
- 31,599 structural variants >50bp (7fold higher than reported)
- 156 inversions per genome

Technological hurdles in diagnostics



Solving the unsolvable diseases

Challenge in Diagnostic Transition:
From genome analysis towards system diagnostics

NeurOmics

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Coordinators:

Olaf Riess & Holm Graessner

„Pilot Project“

Solve-RD - Solving the unsolved Rare Diseases

European Commission | Horizon 2020 European Union funding for Research & Innovation

SolveRD

Solving the unsolved Rare Diseases

Tomorrow‘s diagnostics:

Who should do this?
How should we do this?

Steps to be undertaken to overcome diagnostic hurdles of rare diseases: Role of European Genome Analytic Hubs

„Easy“	National diagnostic centers	...s	Centralized WGS
Advanced	Intn. diagnostic networks	...aking	
Sophisticated	Innovation centers	...lode-ling	Machine learning/AI

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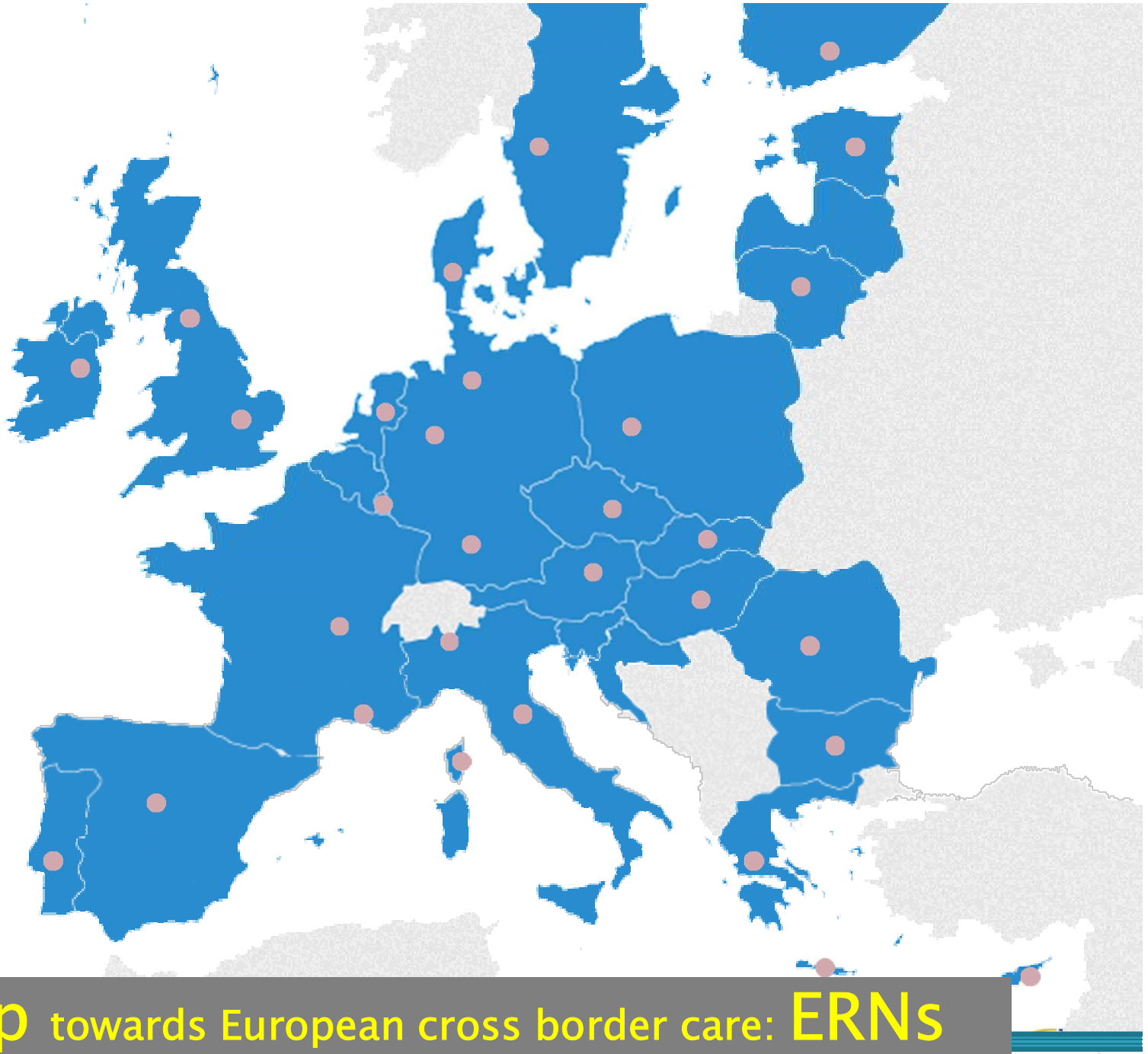
Clinical centers

European Reference Networks

ERN1

ERN2

ERN3



First step towards European cross border care: ERNs

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Clinical centers

European Reference Networks

European Genetic Diagnostic Centers

European Genetic Diagnostic Reference Networks

TECHGENE

RD Connect

ERN1 EGD-RN1

ERN2 EGD-RN2

ERN3 EGD-RN3

- Technical standards of WES -> WGS in diagnostics
- Standardization of bioinformatic tools and algorithms
- Standards in clinical reporting of findings
- „Clearance“ of wrong annotations in data bases
- Harmonization of interpretations of variants (VUS classification)
- Defining „actionable genes“ and implementation in the clinics
- Transcriptome data reference sets
- Multi-Omics in Diagnostics
- Machine learning / Artificial intelligence

Next step towards European cross border care: **EGDRNs**

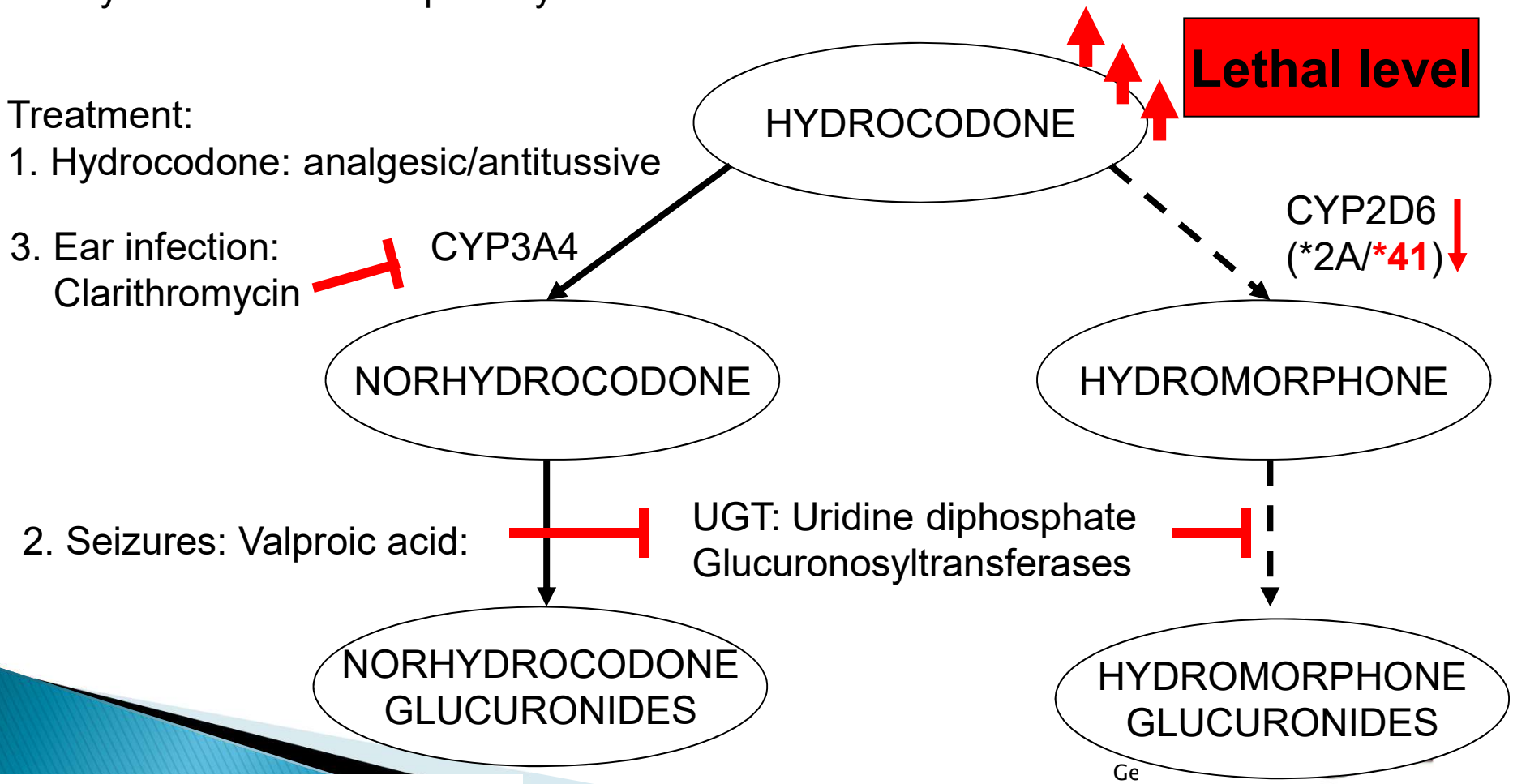
Future developments of Medical Genetics in Medicine?

DISEASE PREDICTION and PREVENTION

Mutation =
Preventing side effects

Pharmacogenetics and drug interactions

6 year old **developmentally delayed child with epilepsy died** after high dose of hydrocodone for respiratory tract infection.

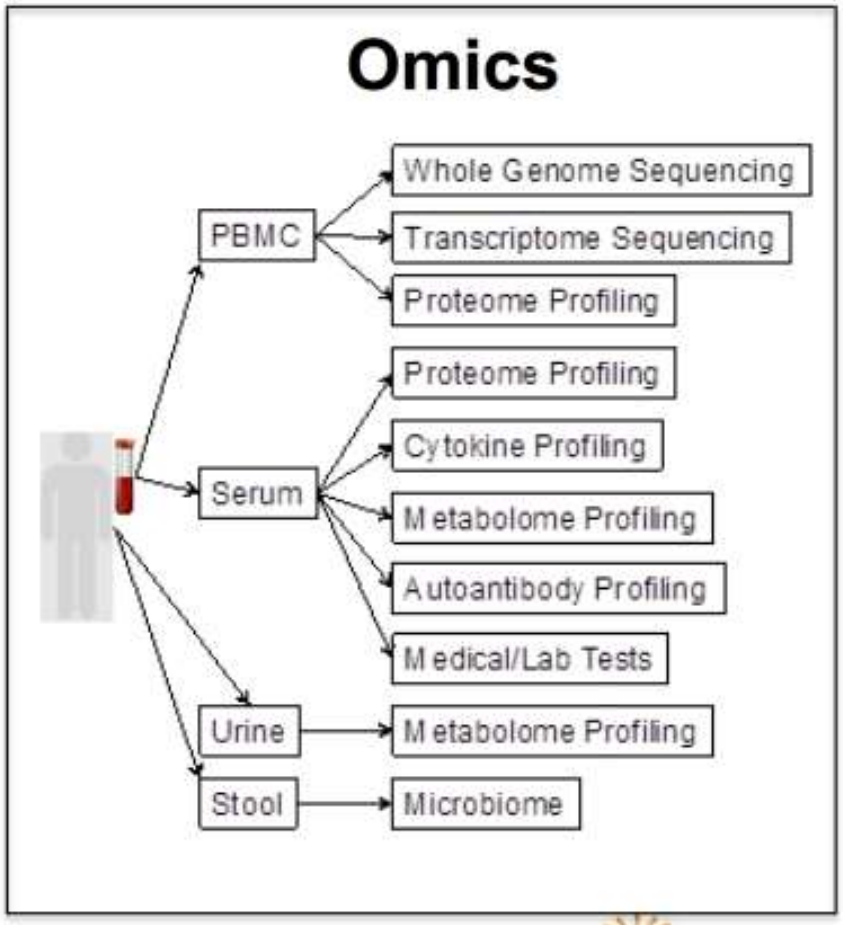


Madadi et al. Pediatrics 2010

ACMG list of actionable genes

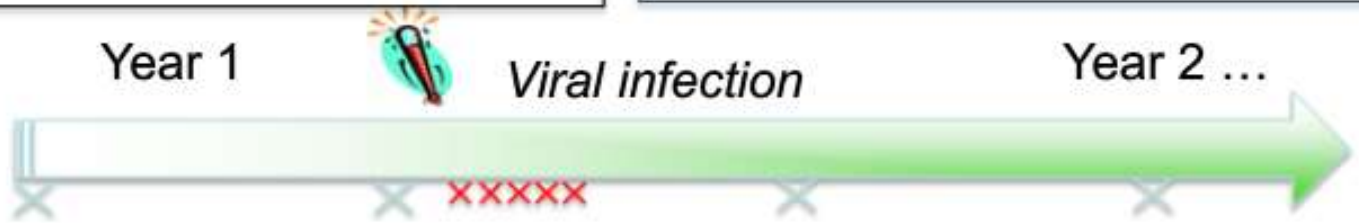
CONDITION	GENES	CLINICAL RISK
HBOC	BRCA1 and BRCA2	Early Breast or Ovarian Cancer
Lynch Syndrome	MLH1, MSH2, MSH6, PMS2	Early Colon or Uterine Cancer
Familial Hyper-cholesterolemia	LDLR, APOB, PCSK9	Early Coronary Artery Disease
Hypertrophic Cardiomyopathy	Multiple genes on list	Cardiac Arrest Heart Transplant

Personal “Omics” Profiling (POP)



Standard Health Panels

Creatinine, Ser/Plas	Calcium, Ser/Plas*	RBC
ALT (SGPT), Ser/Plas	Hematocrit* exercise/ dehydration	MCHC
Potassium, Ser/Plas	Alk P'TASE, Total, Ser/Plas	MCH
Sodium, Ser/Plas	Albumin, Ser/Plas	WBC
AST (SGOT), Ser/Plas	Platelet count*	RDW***
CO2, Ser/Plas*	Hemoglobin	MCV
Chloride, Ser/Plas	Anion Gap**	Glucose,
...	...	...



From Michael Snyder, Stanford

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Zentrum für Seltene Erkrankungen

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I declare no conflict of interest.

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Zentrum für Seltene Erkrankungen

Institut für
Medizinische Genetik und
Angewandte Genomik

Deutschland
Land der Ideen
Ausgewählter Ort 2011