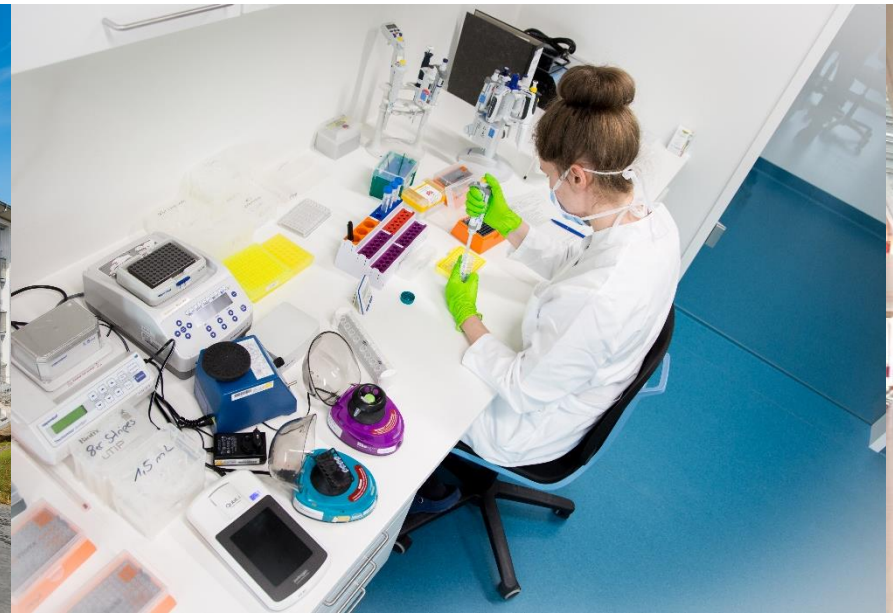
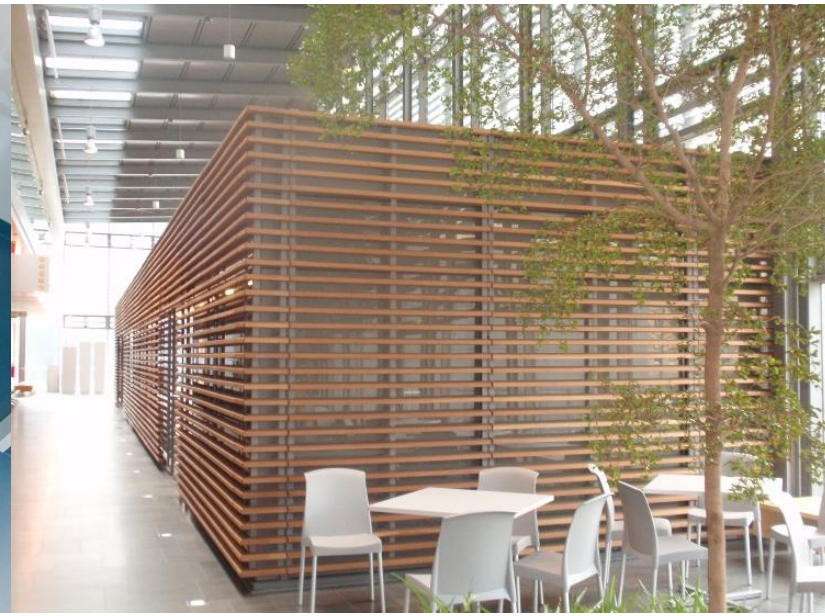
www.uniklinikum-dresden.de
www.tu-dresden.de/med/mf
www.nct-dresden.de

Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

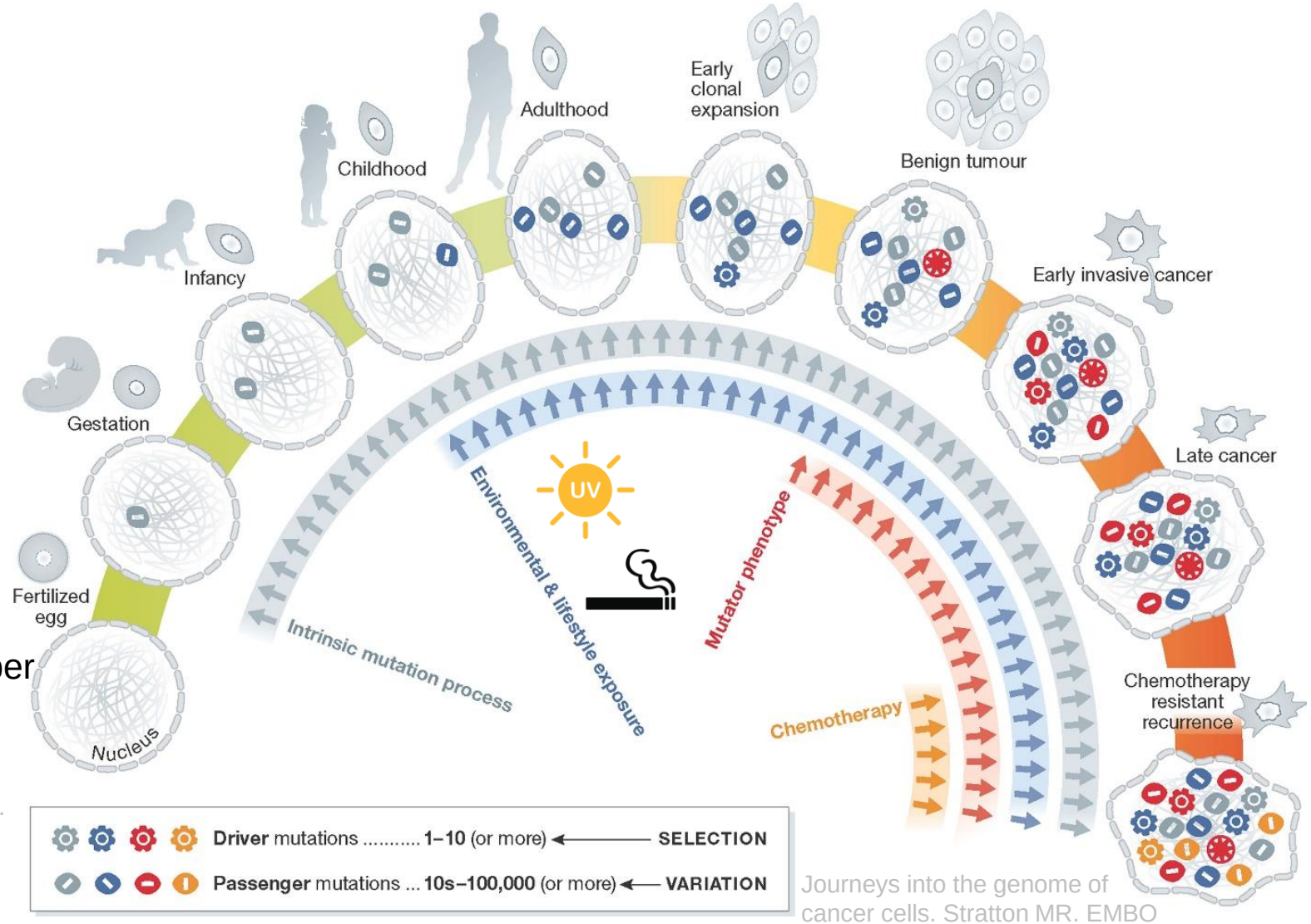
Network for Hereditary Tumor Diseases –

Opportunities for Therapy, Early Detection and Prevention

Prof. Dr. med. Evelin Schröck
Institut für Klinische Genetik, Universitätsklinikum Carl Gustav Carus, TU Dresden
Forschungsgruppe Genetische Tumorrisikosyndrome und
Core Unit für Molekulare Tumordiagnostik (CMTD) am NCT/UCC Dresden

Genetic changes are a hallmark of tumours

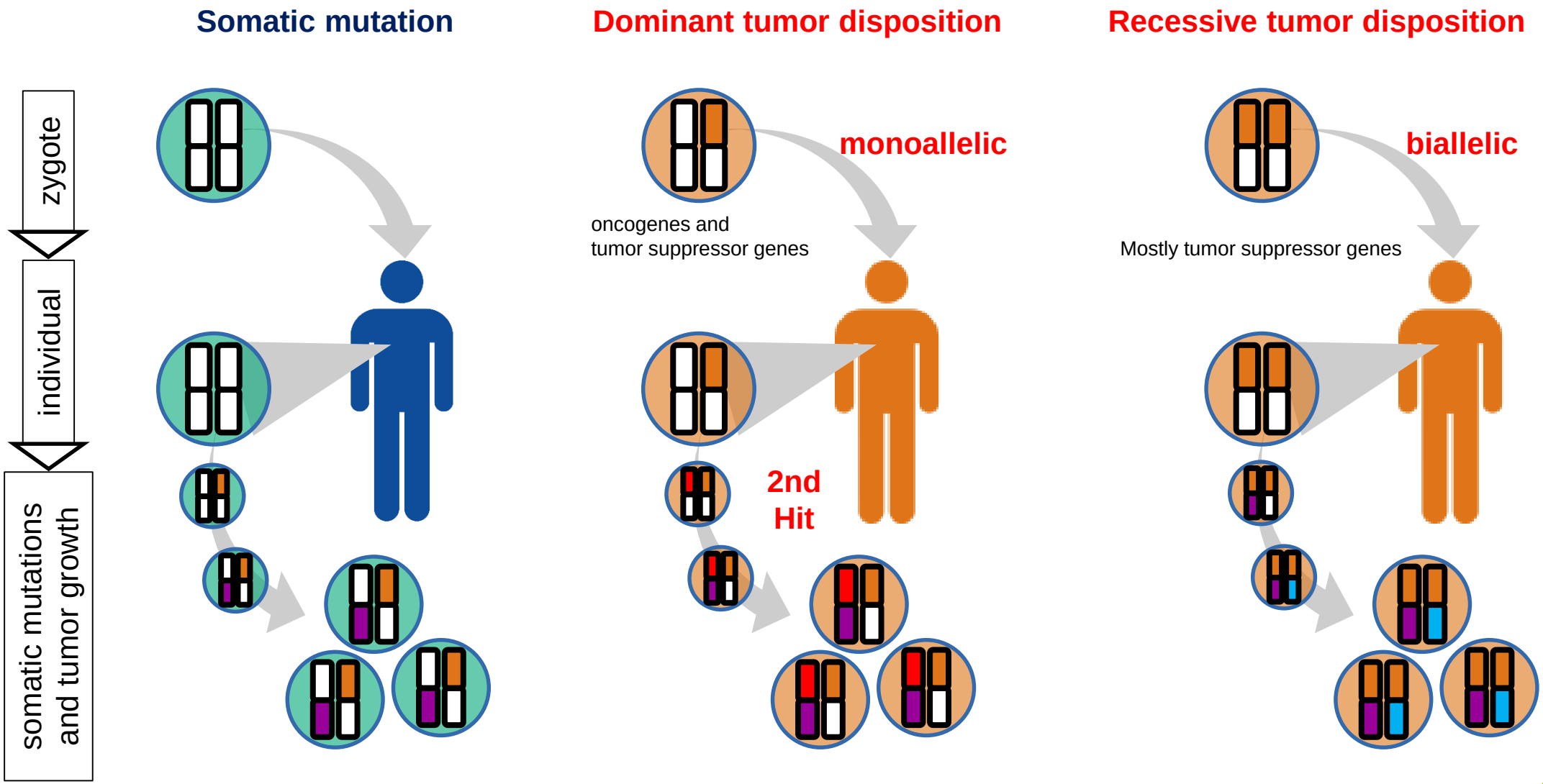


E.g. in average 1.14 variants per cell division in haematopoiesis

Werner *et al.*, *Nat Commun* **11**, 1035 (2020).

Journeys into the genome of cancer cells. Stratton MR. EMBO Mol. Med. 2013

Somatic cancer vs. genetic tumor risk syndromes



Sporadic tumors
→ **no heritability (or complex)**

e.g., Li-Fraumeni Syndrome (TP53)
→ **50% chance of inheritance**

e.g., constitutional mismatch repair deficiency → **100% carrier**

More than 200 genetic tumor risk syndromes – expert networks are needed for diagnostics, clinical management and therapy

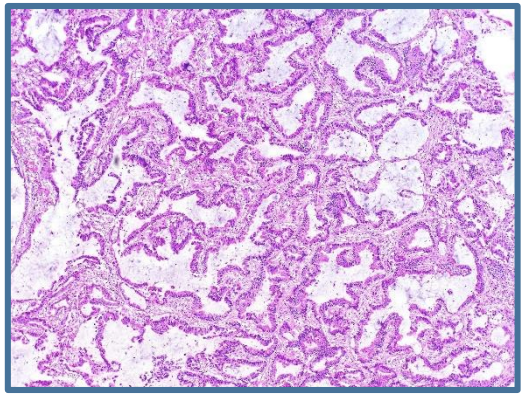
cancer (examples)	syndromes	genes (examples)
Breast cancer	Hereditary Breast and Ovarian Cancer (HBOC)	BRCA1, BRCA2, RAD51C, CHEK2
Colorectal cancer	Lynch-Syndrom	Mismatch-Repair-Genes
Gastric cancer	Hereditary gastric cancer	CDH1
Colorectal polyps	Familial adenomatous polyposis (FAP), aFAP	APC, (MUTYH)
Colorectal polyps	Familial juvenile polyposis	SMAD4, BMPR1A
Gastrointestinal polyps	Peutz-Jeghers syndrome	STK11
Parathyroid cancer	Multiple endocrine neoplasia type 1	MEN1
Medullary thyroid cancer, pheochromocytoma	Familial medullary thyroid cancer	RET, SDH-Gene
Follicular thyroid cancer, Breast cancer	Cowden syndrome	PTEN
Pancreatic cancer	Familial pancreatic cancer	BRCA2, CDKN2A, PALB2
Renal cell carcinoma	Familial renal cell carcinoma	VHL, MET, FH
Wilms‘ Tumor	Wilms´ Tumor	WT1
Sarcomas	Li-Fraumeni syndrome	TP53
Melanoma	Familial malignant melanoma, FAMMM	CDKN2A, CDK4, BRCA2, XP-Gene
Neurofibromatosis	Neurofibromatosis Typ 1	NF1
Vestibular schwannoma	Neurofibromatosis Typ 2	NF2
Retinoblastoma	Retinoblastoma	RB

NCT

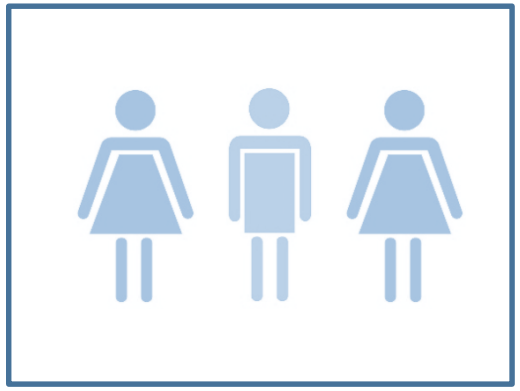
nNGM Lung Cancer Task Force 5 Genetic Tumor Risk

nNGM | Nationales Netzwerk Genomische Medizin Lungenkrebs

- Known risk factors are occupational and environmental risk factors (e.g. passive smoking, radon and air pollution)
- 10–15% of lung cancers occur in never-smokers, number increasing
- Lung cancer in never-smokers distinct from smoking related cancer



Histology
adenocarcinomas



Epidemiology
⅔ women

Genomics & Genetics
targetable oncogenic alterations
& low / absent PD-L1 expression

Current status of germline genome sequencing

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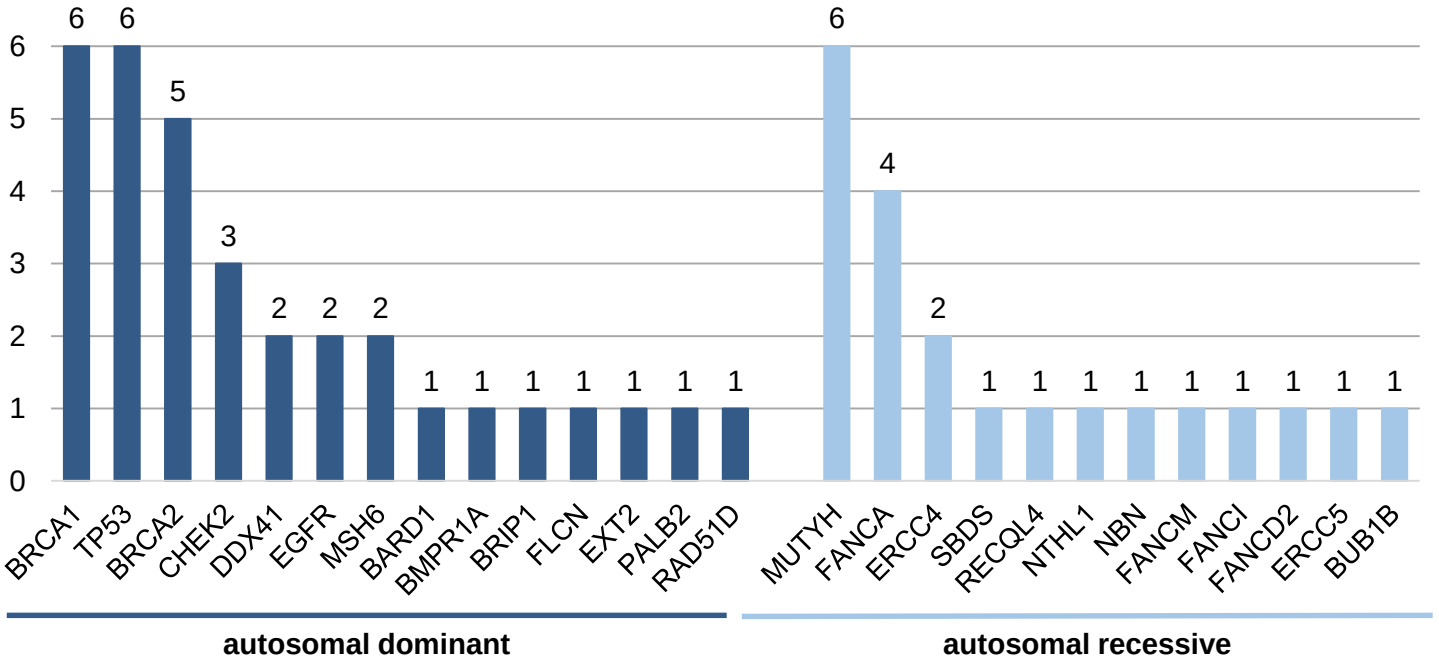
- 347 samples sequenced and analyzed
- 1 genetic report pending
- 3 samples waiting for validation
- 32 sequencing analyses pending

  - 33 (9,5%) heterozygous pathogenic **autosomal dominant** germline variants
  - 21 (6,1%) heterozygous pathogenic **autosomal recessive** germline variants
  - Rare variants of uncertain significance (VUS) with unclear clinical relevance



nNGM TF5 – Study Cohort

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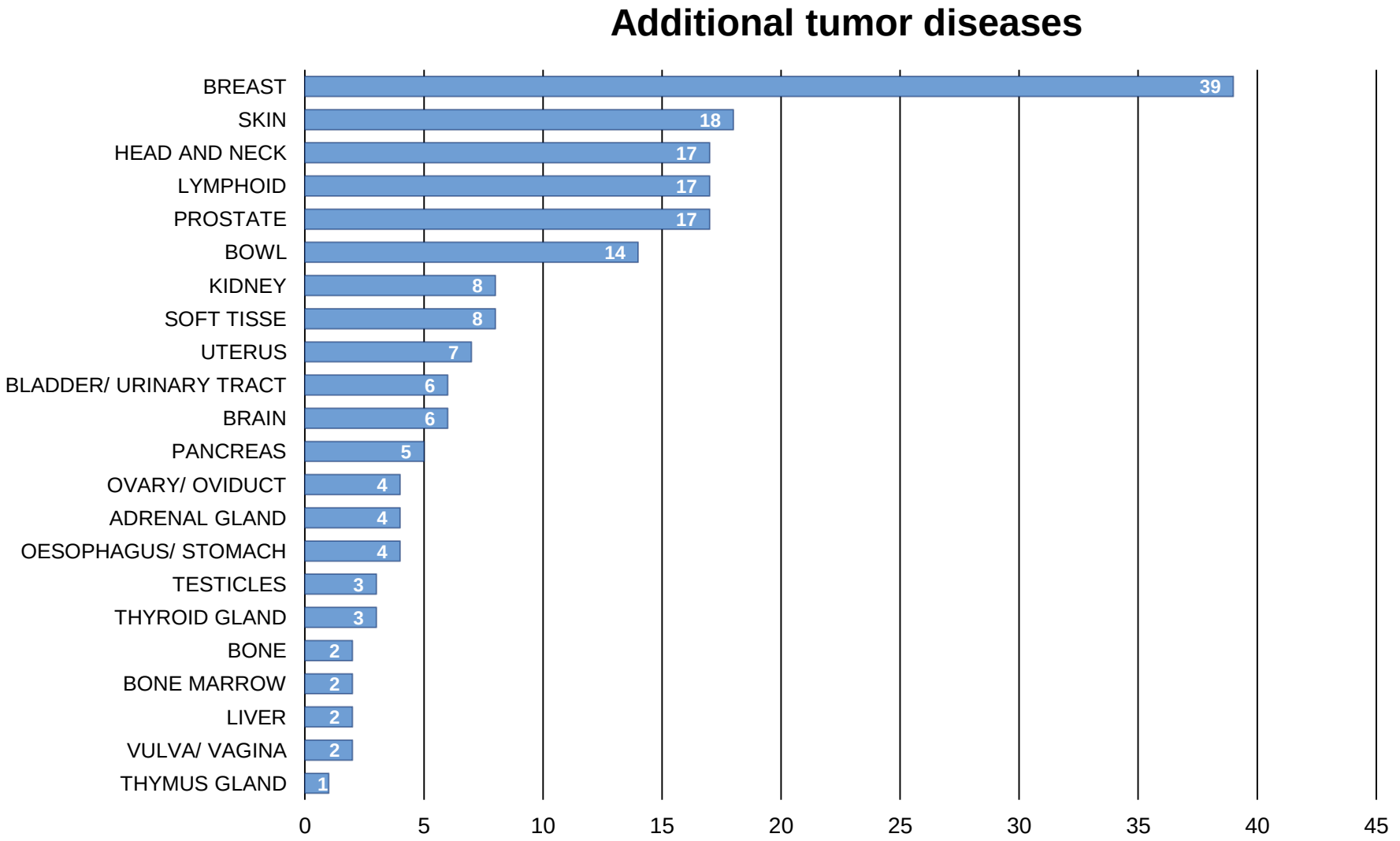

TP53 patient example

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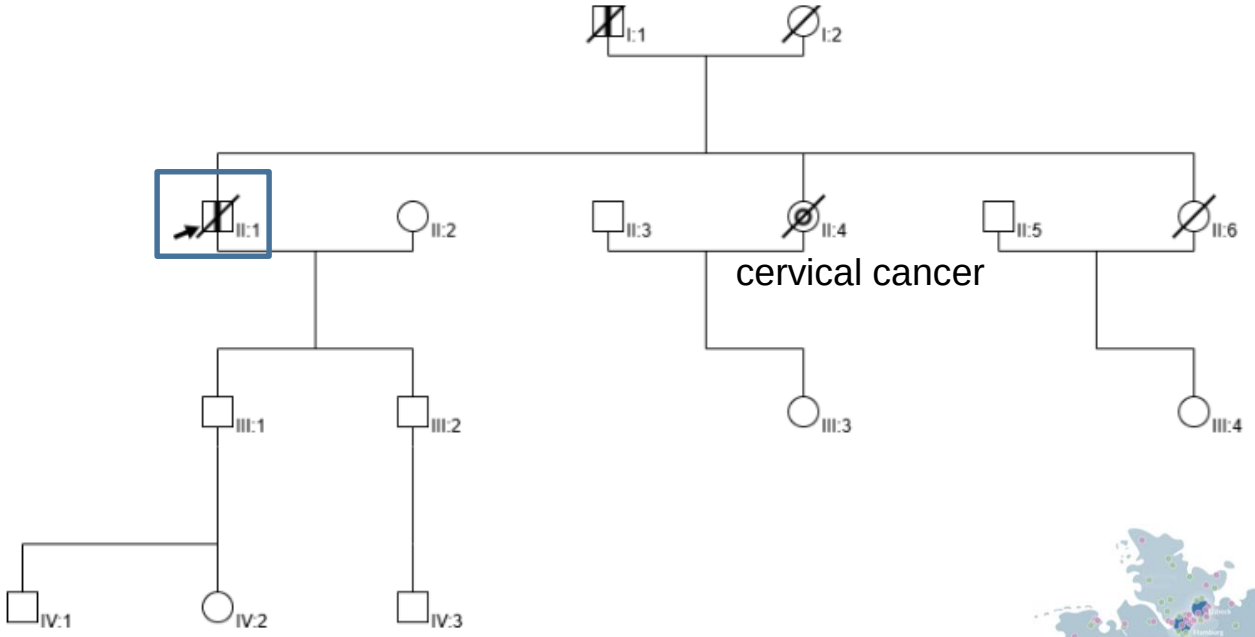
Patient information

- Male, non-small cell lung cancer (63 y)
- Never-smoker
- prostate carcinoma (AO 57 years),
- renal cell carcinoma (AO 57 years)
- Family history:
  - father with lung cancer
  - sister with cervical cancer



Variant information

- NM_000546.6:c.743G>A, p.(Arg248Gln), heterozygous
- Exon 7 of 11
- gnomAD n=12
- ACMG criteria: PM1, PP3, PS3, PS4, PS2

Clinical consequences

- Diagnosis: Li-Fraumeni syndrome

ESHG Milan 2025, Li-Fraumeni syndrome
E. Kasper et al, Rouen

- Sperm donor for at least 67 children
- 23 with *TP53* pathogenic variant
- 10 children dianosed with cancer so far

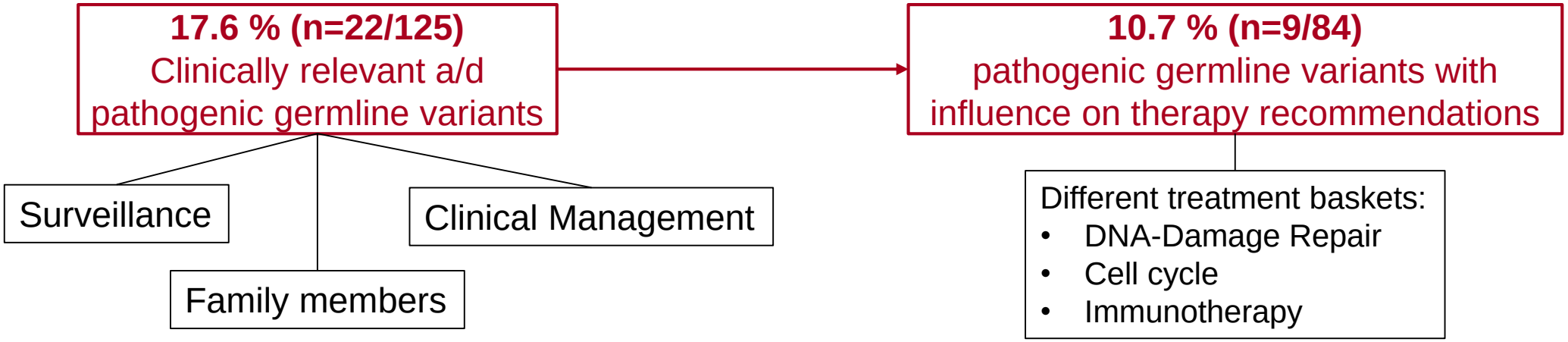
Parallel Molecular Genetic Analysis of Tumor and Germline: Multiple Benefits

Patients with **pancreatic cancer** from the DKFZ/NCT/DKTK–MASTER Program (n=84):

- Improved interpretation of variants of unknown significance through information from tumor analysis (LOH)

Patients with **pancreatic cancer** from our institute referred by physicians best choice (n=41):

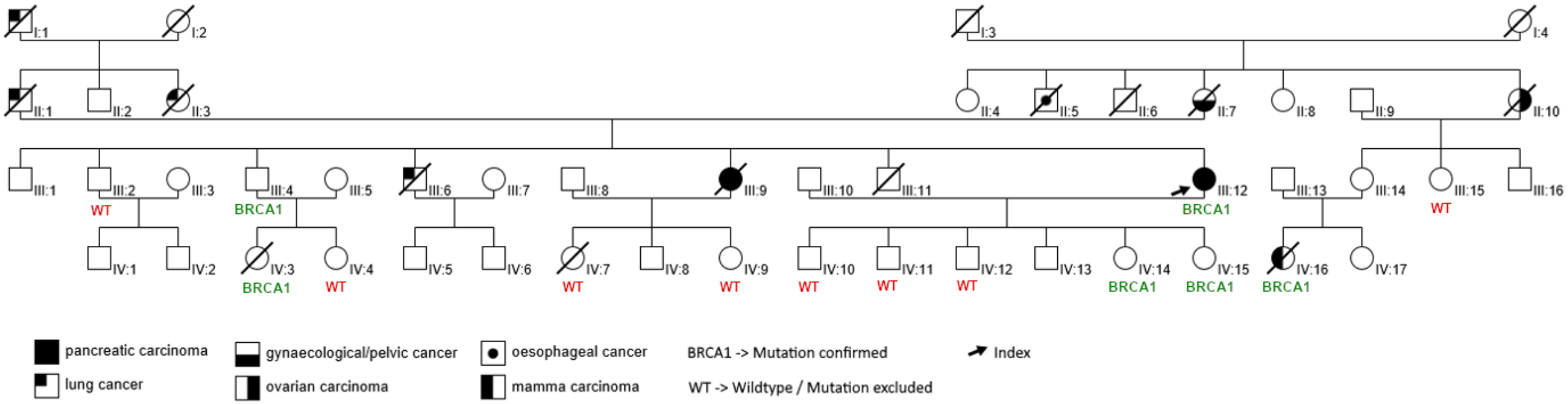
- Comprehensive pedigree information



23.5 % (n=4/17) of PCA patients with an autosomal dominant GENTURIS did not meet the German S3-Guideline recommendations for genetic testing.

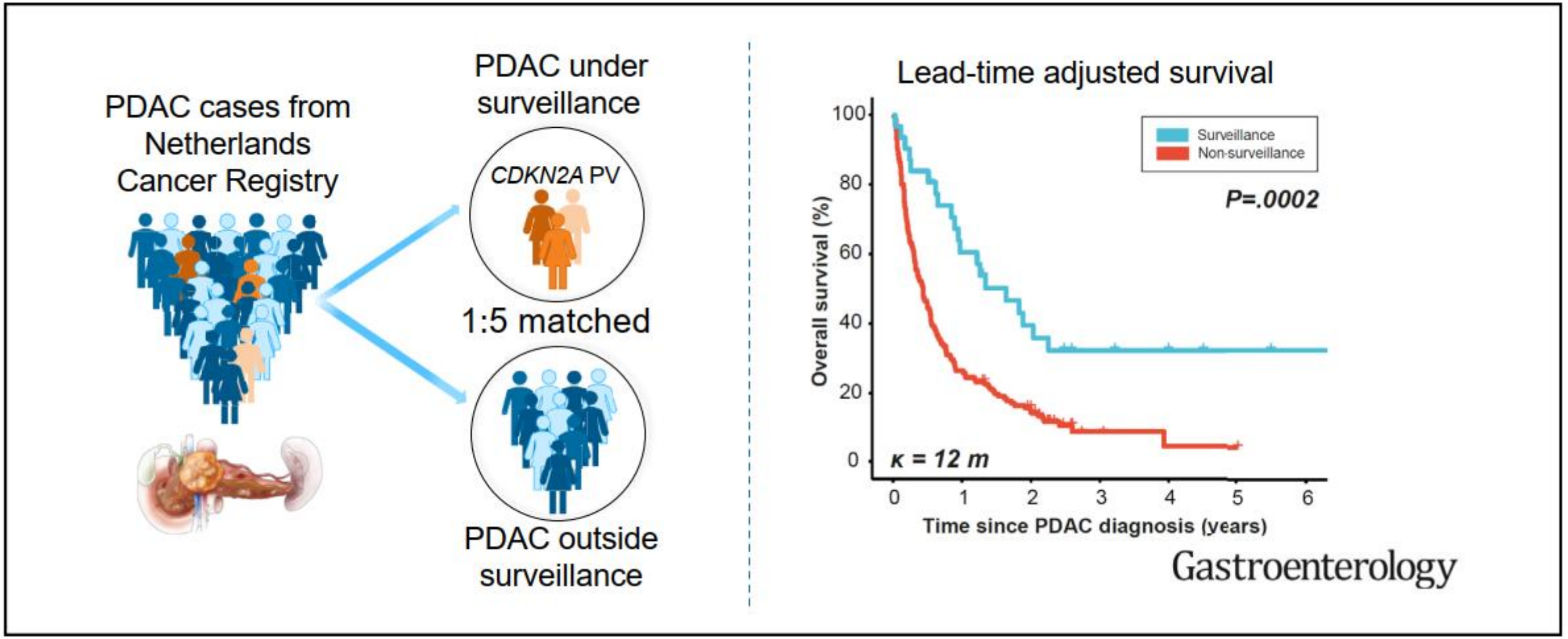
Hereditary vs. Sporadic Pancreatic Cancer –

- personal and family history → pedigree evaluation
- age of onset, cancer entity and histology
- Genetic testing based on inclusion criteria (S3 guideline pancreatic cancer) → index patient – not to be tested, 6 children and siblings could have been tested



William et al., ESMO Gastroenterology accepted

Surveillance for pancreatic adenocarcinoma in carriers of a *CDKN2A/p16* pathogenic variant results in earlier detection, increased resectability, and improved survival as compared with non-surveillance patients



Derk C. F. Klatte et al., Gastroenterology 2023;164:1223–1231

Personalized therapeutic options based on (likely) pathogenic germline variants in gentic tumor syndromes

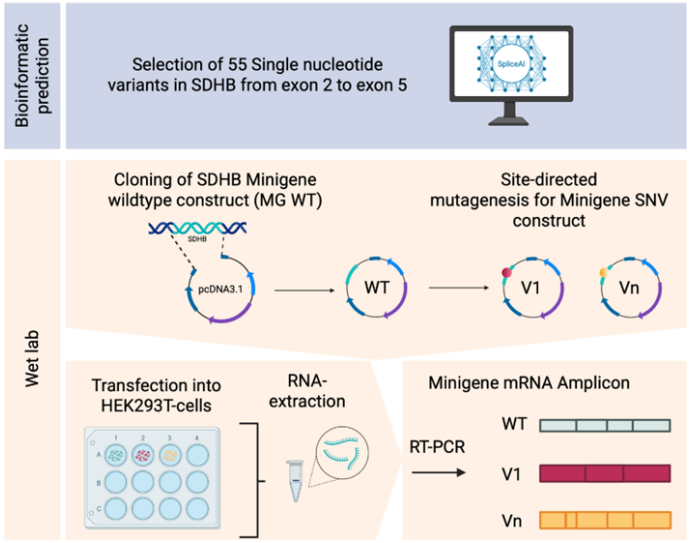
Gene(s)/alteration*	Entity/ phenotype	Mechanism of action	Drug
BRCA1/2	HER2-negative metastasized breast cancer, Platinum sensitive high-grade ovarian cancer, Platinum sensitive metastatic pancreatic adenocarcinoma	PARP-inhibitor	Olaparib Talazoparib Rucaparib
BRCA1/2 (and e.g. ATM, BRIP1, BARD1, CHEK2, FANCL, PALB2, RAD51C, RAD51D*)	Metastatic castration-resistant prostate cancer	PARP-inhibitor	Olaparib Rucaparib (Talazoparib)
MSI-high TMB-high (Lynch syndrome, POLD/E?)	Solid tumors	checkpoint inhibitor (Anti-PD-1 antibody)	Pembrolizumab Ipilimumab Nivolumab
NF1	Pediatric inoperable plexiform neurofibromas	MEK ½ inhibitor	Selumetinib
VHL	Von Hippel-Lindau (VHL) disease and tumors; renal cell carcinoma	HIF-2α-Inhibitor	Belzutifan
RET	(Medullary) thyroid cancer	selective RET inhibitors	Selpercatinib Pralsetinib
PTCH1, SUFU	Basal-cell nevus syndrome associated basal cell carcinoma	Hedgehog Pathway Inhibitor	Vismodegib Sonidegib
EGFR	Lung cancer	tyrosine kinase (EGFR) inhibitors	Osimertinib and others
KIT/PDGRF	Gastrointestinal stroma tumors	tyrosine kinase (KIT/PDGRF) inhibitors	Imatinib and others
PTEN	Breast cancer, vascular malformations	mTOR/AKT-inhibitors	e.g. Sirolimus, Capivasertib
TSC1/2	TSC-associated angiofibroma, partial-onset seizures, subependymal giant cell astrocytoma, lymphangioleiomyomatosis and renal angiomyolipoma	mTOR-inhibitors	Sirolimus/ Everolimus
PIK3CA	severe manifestations of PIK3CA-related overgrowth spectrum	PIK3CA-inhibitor	Alpelisib

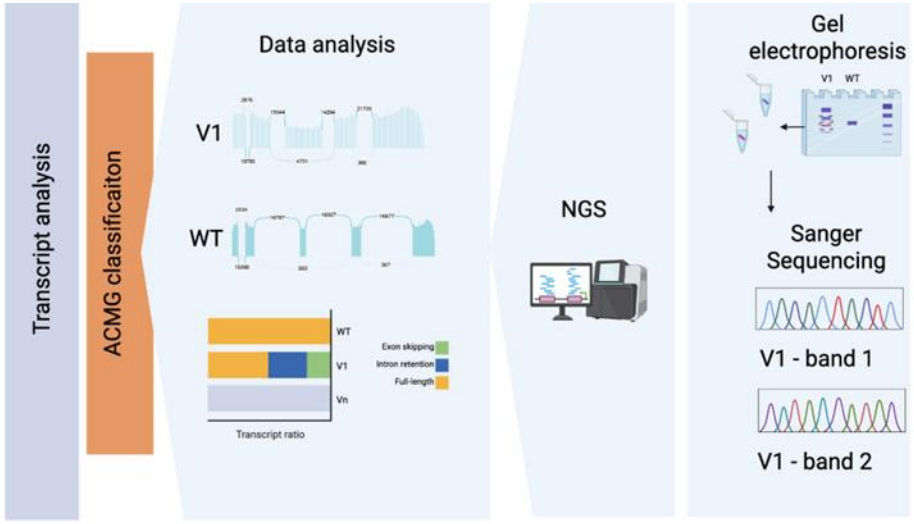
Jahn et al., medizinischegenetik submitted

NCT

Research Projects: Variant Classification and Disease Mechanisms

Mini-Gene assays to classify so far undefined splice variants

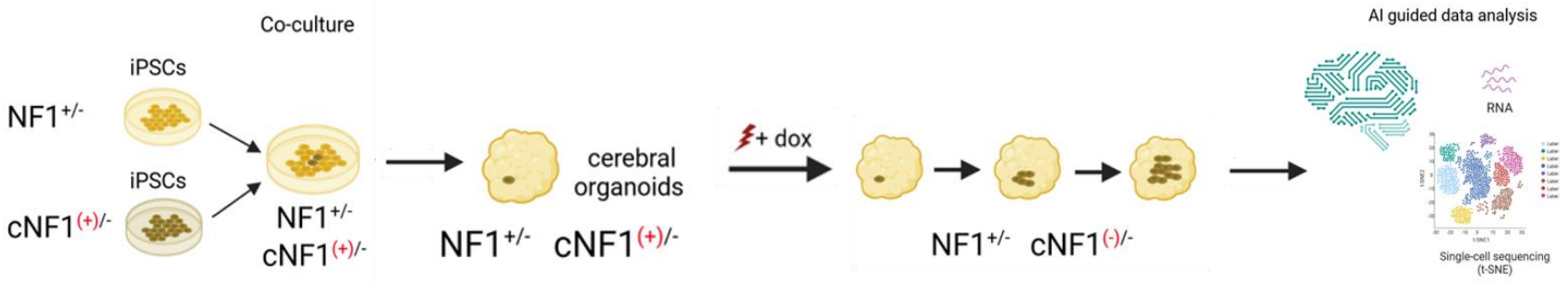




Jahn et al.

Patient Derived Organoid Models and single cell multi-omics: early tumorigenesis of *NF1*-associated brain cancer

Simulation of a second hit event in NF1 in patient-derived cerebral organoids.



GILBERT FAMILY FOUNDATION

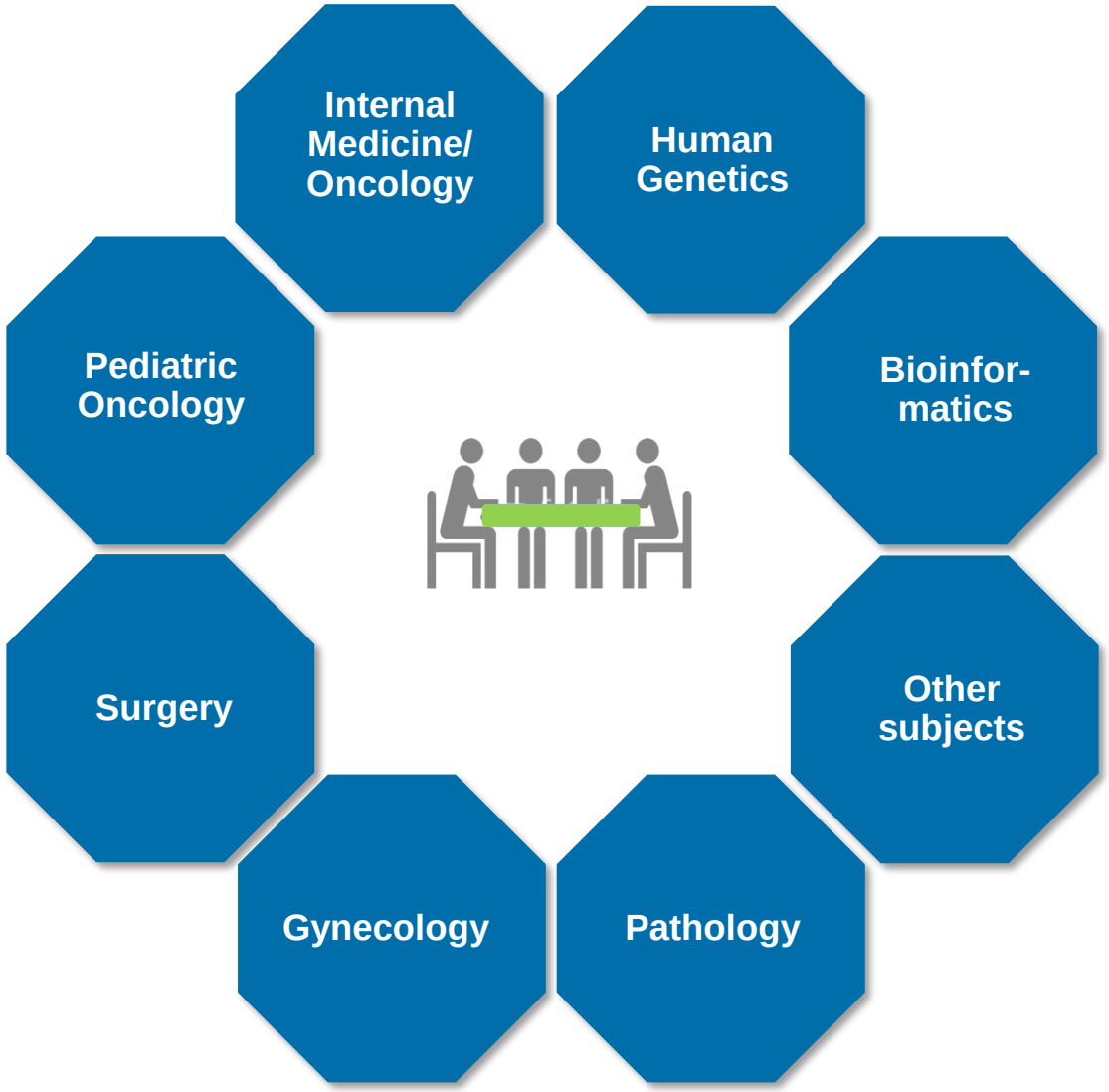
William et al.

Cooperations: Anna Poetsch (CMCB), David Solomon (Stanford)

Strong increase of patient numbers is expected

Cancer type	% hereditary	Literature
Pancreatic cancer (20.000 pro Jahr)	**19,8 %** **14,1 %** **18,1 %** **16,6 %** **21,6 %**	doi: 10.1093/jnci/djy024 / PMID: 29506128 Lowery et al. J. Natl Cancer Inst. 2018 doi: 10.1002/cam4.2973 / PMID: 32255556 Cremin et al. Cancer Med. 2020 doi: 10.3390/cancers13174430 / PMID: 34503238 Wieme Cancers (Basel) 2021 doi: 10.3390/cancers14184447 / 36139606 Puccini et al. Cancers (Basel) 2022 William et al., accepted
Sarcoma (5.000 pro Jahr)	**11,4 %** **12,5 %** **6,6 %** **21,5 %**	doi: 10.1016/j.annonc.2022.07.008 / PMID: 35988656 Jahn et al. Ann Oncol 2022 doi: 10.1016/j.cell.2018.03.039 / PMID: 29625052 Huang et al. Cell 2018 doi: 10.1126/science.abj4784 / PMID: 36656928 Ballinger et al. Science 2023 doi: 10.1136/jmg-2023-109269 / PMID: 37536918 De Angelis de Carvalho et al. Cancer Genetics 2023
Leiomyosarcoma (rare)	**16,5 %**	doi: 10.1016/j.annonc.2022.07.008 / PMID: 35988656 Jahn et al. Ann Oncol 2022
Thymus epithelial cancer (rare)	**1 %** **25 %** **30 %**	doi: 10.1038/s41525-019-0087-6 / PMID: 31263571 Bertelsen et al., NPJ Genom Med 2019 doi: 10.1158/1538-7445.AM2023-926 Möhrmann L Cancer Res (7_Supplement) 2023 doi: 10.3390/cancers14143388 / PMID: 35884448 Szpechcinski et al Cancers (Basel) 2022
Cancer of unknown primary (6.400 per year)	**2 %** **8,3 %** **2,8 %** **7,2 %**	doi: 10.1038/s41525-019-0087-6 / PMID: 31263571 Bertelsen et al., NPJ Genom Med 2019 doi: 10.3390/ijms24054302 / PMID: 36901733 Vanni et al., Int. Mol. Sci. 2023 doi: 10.1016/j.annonc.2022.07.008 / PMID: 35988656 Jahn et al. Ann Oncol 2022 Doi: 10.1038/s41467-022-31866-4 / PMID: 35918329 Möhrmann et al. Nat Commun 2022

Multidisciplinary case conference – Molecular Tumor Board



UniversitätsCentrum für Seltene Erkrankungen

USE - Zentrum für Klinische Genommedizin

achse
Allianz Chronischer Seltener Erkrankungen

NAMSE
Zertifiziertes Zentrum für Seltene Erkrankungen

European Reference Network
for rare or low prevalence complex diseases
Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

ZPMO Dresden
Zentrum Dresden

Deutsches Konsortium Familiärer Brust- und Eierstockkrebs
Etabliert durch die Deutsche Krebshilfe
Zentrum Dresden

Deutsches Konsortium Familiärer Darmkrebs

DKFZ/NCT/DKTK MASTER Program

nNGM | Nationales Netzwerk Genomische Medizin Lungenkrebs

genomDE

gfh
Netzwerk Erbliche Tumorerkrankungen

dnpm
Deutsches Netzwerk für Personalisierte Medizin

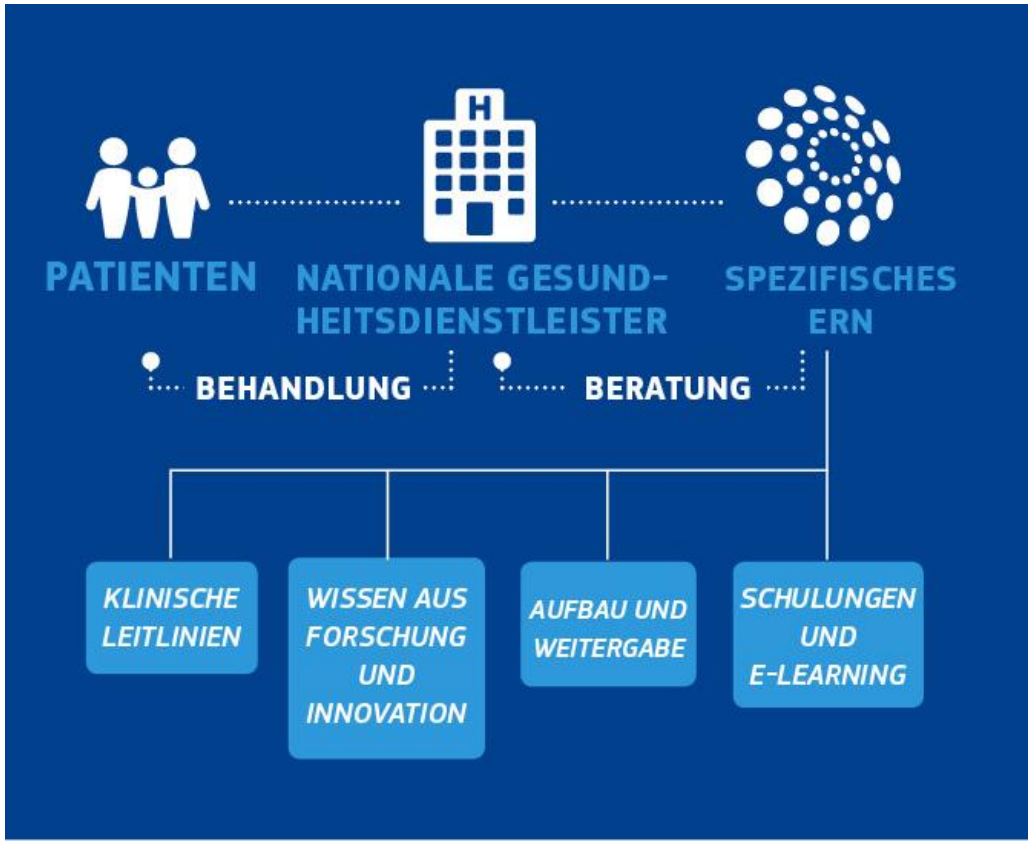
Zentren im Netzwerk GfH-ET

Modellvorhaben Genomsequenzierung nach § 64e SGB V, GKV-SV 26.05.2025	
Bereich Seltene Erkrankungen	**Bereich Onkologische Erkrankungen**
Universitätsklinikum Aachen	Universitätsklinikum Aachen
Charité - Universitätsmedizin Berlin	Charité - Universitätsmedizin Berlin
Universitätsklinikum der Ruhr – Universität Bochum	Universitätsklinikum Bonn
Universitätsklinikum Bonn	Universitätsklinikum Carl Gustav Carus Dresden
Universitätsklinikum Carl Gustav Carus Dresden	Universitätsklinikum Düsseldorf
Universitätsklinikum Düsseldorf	Universitätsklinikum Erlangen
Universitätsklinikum Erlangen	Universitätsklinikum Freiburg
Universitätsklinikum Essen	Universitätsklinikum Gießen und Marburg – Standort Gießen
Universitätsklinikum Freiburg	Universitätsmedizin Göttingen
Universitätsmedizin Göttingen	Universitätsklinikum Halle (Saale)
Universitätsklinikum Hamburg - Eppendorf	Universitätsklinikum Hamburg – Eppendorf
Medizinische Hochschule Hannover (MHH)	Medizinische Hochschule Hannover (MHH)
Universitätsklinikum Heidelberg	Universitätsklinikum Heidelberg
Universitätsklinikum Jena	Universitätsklinikum Jena
Universitätsklinikum Köln	Universitätsklinikum Köln
Universitätsklinikum Leipzig	Universitätsmedizin der Johannes Gutenberg-Universität Mainz
LMU Klinikum München	Universitätsklinikum Gießen und Marburg – Standort Marburg
Klinikum der Technischen Universität München (TUM Klinikum)	LMU Klinikum München
Universitätsklinikum Münster	Klinikum der Technischen Universität München (TUM Klinikum)
Universitätsklinikum Regensburg	Universitätsklinikum Münster
Universitätsklinikum Tübingen	Universitätsklinikum Regensburg
Universitätsklinikum Schleswig-Holstein	Universitätsklinikum Tübingen
Universitätsklinikum Ulm	Universitätsklinikum Schleswig-Holstein
Universitätsklinikum Würzburg	Universitätsklinikum Ulm
	Universitätsklinikum Würzburg

Network for hereditary cancer – goals

- Raise Awareness for genetic tumor syndromes: doctors, patients, public
- Improve diagnostic procedures: whole genome sequencing, Long-read sequencing, Multi-omics, Quality Management
- Perform case discussions
- Collect data in registry and cohorts for research
- Continously Re-evaluate and improve inclusion criteria
- Expand and improve therapeutic strategies
- Manage psychosocial and psychoeconomic consequences
- Perform cascade testing
- Perform research projects
- Interact with all networks and experts

ERN-GENTURIS - European Reference Network for Clinical Care and Research for Patients with Genetic Tumor Risk Syndromes



- Virtual networks of healthcare providers with the active participation of patient representatives
- 23 EU countries, 52 centers, increasing
- Pool of expertise on complex or rare diseases, virtual case conferences
- Guidelines (TP53, PTEN, NF1, schwannomatosis, GIST, sarcomas), research, registers
- Research project: paragangliomas (cooperation: Susan Richter (MK3))

European Reference Network
for rare or low prevalence complex diseases
Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

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Institut für Klinische Genetik

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Mareike Albert
Andreas Dahl (DRESDEN-concept Genome Center)

Center for Systems Biology Dresden (CSBD)

Eugene Myers

European Reference Network for rare or low prevalence complex diseases
Network Genetic Tumour Risk Syndromes (ERN GENTURIS)

nNGM Koordinationsteam

Christof von Kalle (Berlin)
Reinhard Büttner (**Köln**)
Jürgen Wolf (Köln)

nNGM Task Force 5

Speaker:
Evelin Schröck (**Dresden**), Reinhard Büttner (**Cologne**), André Reis (**Erlangen**)
Coordinator Working Group:
Stefan Gattenlöhner (**Giessen**)
Members:
Ulrich Keilholz (Berlin), Sebastian Thiel (Berlin), Maike de Wit (Berlin), Evelin Schröck (Dresden), Felix Saalfeld (Dresden), Sarah Wölffling (Dresden), Andrea Meinhardt (Dresden), Christina Neppl (Duesseldorf), Arndt Hartmann (Erlangen), André Reis (Erlangen), Yasmin Zaun (Essen), Melanie Demes (Frankfurt am Main), Martin Werner (Freiburg), Judith Fischer (Freiburg), Stefan Gattenlöhner (Gießen), Claudia Wickenhauser (Halle), Corinna Leischner (Hamburg), Janna-Lisa Velthaus (Hamburg), Alexander Volk (Hamburg), Ludwig Wilkens (Hannover), Carolin Plöger (Heidelberg), Sonja Loges (Heidelberg), Hannah Goldschmid (Heidelberg), Reinhard Büttner (Sprecher) (Köln), Axel Hillmer (Köln), Sabine Merkelbach-Bruse (Köln), Patrick Basitta (Bonn), Verena Tischler (Bonn), Jutta Kirfel (Lübeck), Daniel Pieh (Mainz), Frederick Klauschen (Munich), Balazs Jori (Oldenburg), Margit Klier-Richter (Regensburg), Daniela Hirsch (Regensburg), Falko Fend (Tübingen), Irina Bonzheim (Stuttgart), Reiner Siebert (Ulm), Horst Hummel (Würzburg), Katja Maurus (Würzburg)

Thank You Very Much!

Institut für Pathologie

Gustavo Baretton
Daniela Aust

NCT-CMTD

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Daniel Huebschmann
Barbara Hutter
Nagarajan Paramasivam
Katrin Pfütze

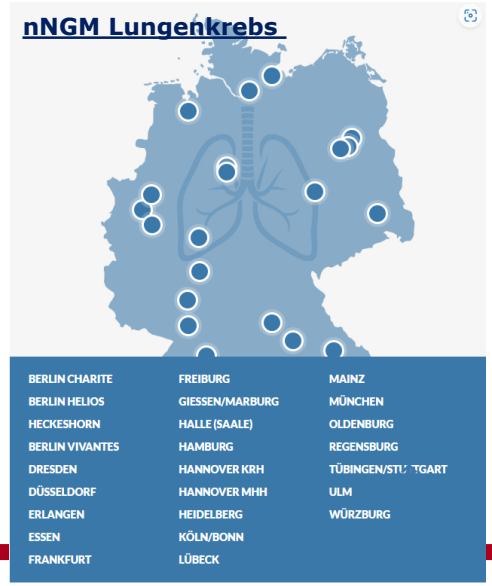
TU München

Annika Schneider
Bernhard Küster

NCT/DKTK MASTER program

All Partner Sites
Many others

nNGM Lungenkrebs



Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Europa fördert Sachsen.
ESF Europäischer Sozialfonds
Gefördert aus Mitteln der Europäischen Union
SACHSEN

DFG Deutsche Forschungsgemeinschaft

Bundesministerium für Bildung und Forschung

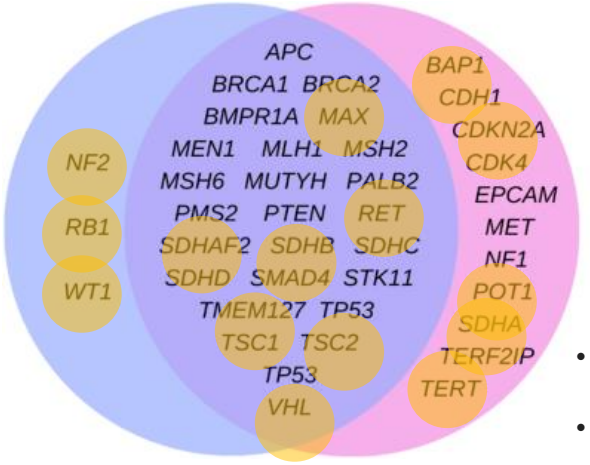
dkfz.
Deutsches Konsortium für Translationale Krebsforschung
Partnerstandort Dresden

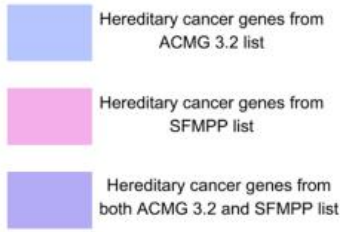
Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

Increasing sequencing is expected to increase GENTURIS diagnoses and there are opportunities to improve clinical care

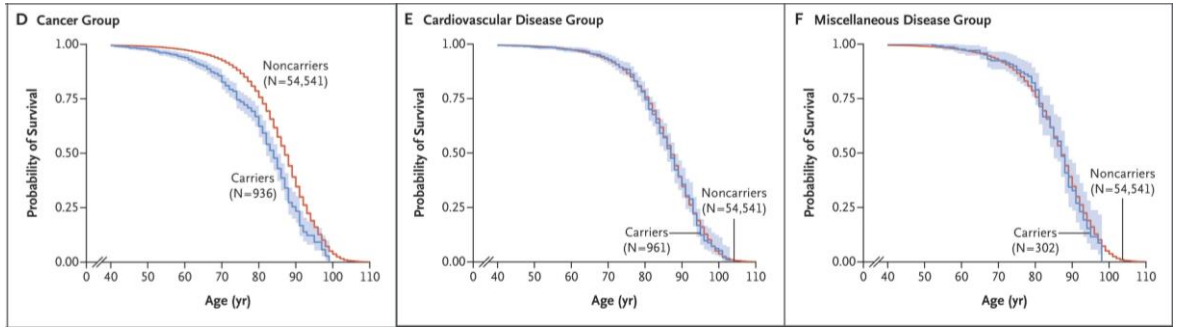
Soll die

- The American College of Medical Genetics and Genomics recommends reporting of cancer related secondary findings in exome/ genome sequencing with a different indication





- American College of Medical Genetics and Genomics (ACMG)
- French Society of Predictive and Personalized Medicine (SFMPP)



Jensson, B.O. *et al.* (2023) 'Actionable Genotypes and Their Association with Life Span in Iceland', *New England Journal of Medicine.*

- Of the 57,933 Iceland participants, 2306 (4.0%) carried at least one actionable genotype.
- carrying an actionable genotype in a cancer gene was associated with survival that was 3 years shorter than that among noncarriers, with causes of death among carriers attributed primarily to cancer-related conditions.

Avsec, E. et al. Secondary findings in hereditary cancer genes after germline genetic testing – systematic review of literature. *Hum. Genet.* **144**, 595–604 (2025).