Molecular genetic diagnostics in breast cancer patients: Insights from a real life cohort

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Conflict of interest

- Full-time employee at the Center for Human Genetics in Tübingen, Germany

- Nothing to declare

Patient cohort from Germany and other countries

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- The Center for Human Genetics in Tübingen (~200 staff) offers a broad range of molecular genetic diagnostics with a focus on cancer and rare diseases (CLIA certified)
- We offer **germline testing** and **somatic tumour diagnostics**
- Our patients are counselled directly in Tübingen and we receive additional samples from German hospitals and private clinics
- Samples from international patients are also part of the cohort provided by our partner:
  Center for Genomics and Transcriptomics

CeGaT

Germline & somatic diagnostic testing

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- **Germline diagnostic** testing for 3719 cancer patients since 2016
  - Including 1024 breast cancer patients (~27%)
- **Somatic diagnostic** testing for 7426 cancer patients since 2018
  - Including 948 breast cancer patients (~13%)
- All germline cases received either panel (>120 genes) or exome sequencing (WES)
- All somatic diagnostics are based on tumour:normal comparison (>700 gene panel or WES)

Germline diagnostics

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- Diagnostic yield is defined as an ACMG/ACGS class 4/5 variant is detected (likely pathogenic (LP) / pathogenic (P))
- *BRCA1+2:* 6.45% yield
- Core genes (sum total): 11.23% yield
- Another 5.83 % cases had LP/P variants in other genes!
- Remark: Our center is not specialized in HBOC patient care; hence our cohort is not enriched in familial HBOC cases!

Core genes

BRCA2
BRCA1
CHEK2
ATM
PALB2
BRIP1
BARD1
RAD51C
RAD51D
TP53
CDH1
NF1
PTEN
STK11

Germline diagnostics

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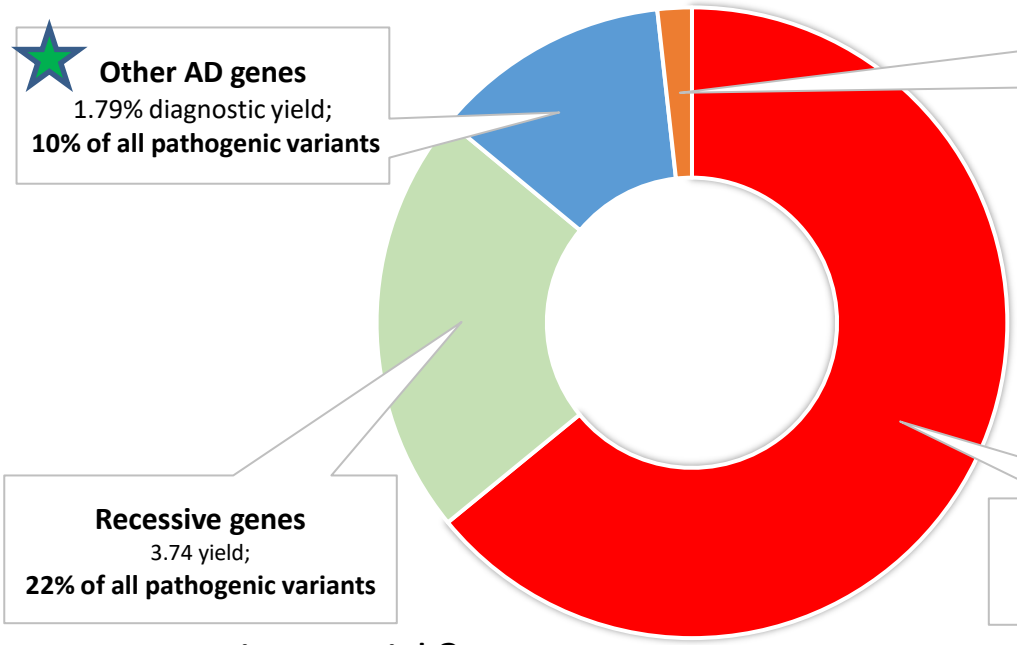
Distribution of pathogenic variants among gene groups



Other AD genes
1.79% diagnostic yield;
10% of all pathogenic variants

Lynch-Syndrome
0.3% diagnostic yield;
2% of all pathogenic variants

+ 2.1% potential differential diagnosis!

HBOC Core Genes
11.23% diagnostic yield;
66% of all pathogenic variants

?

Recessive genes
3.74 yield;
22% of all pathogenic variants

Heterozygous carriers at risk?

Germline diagnostics

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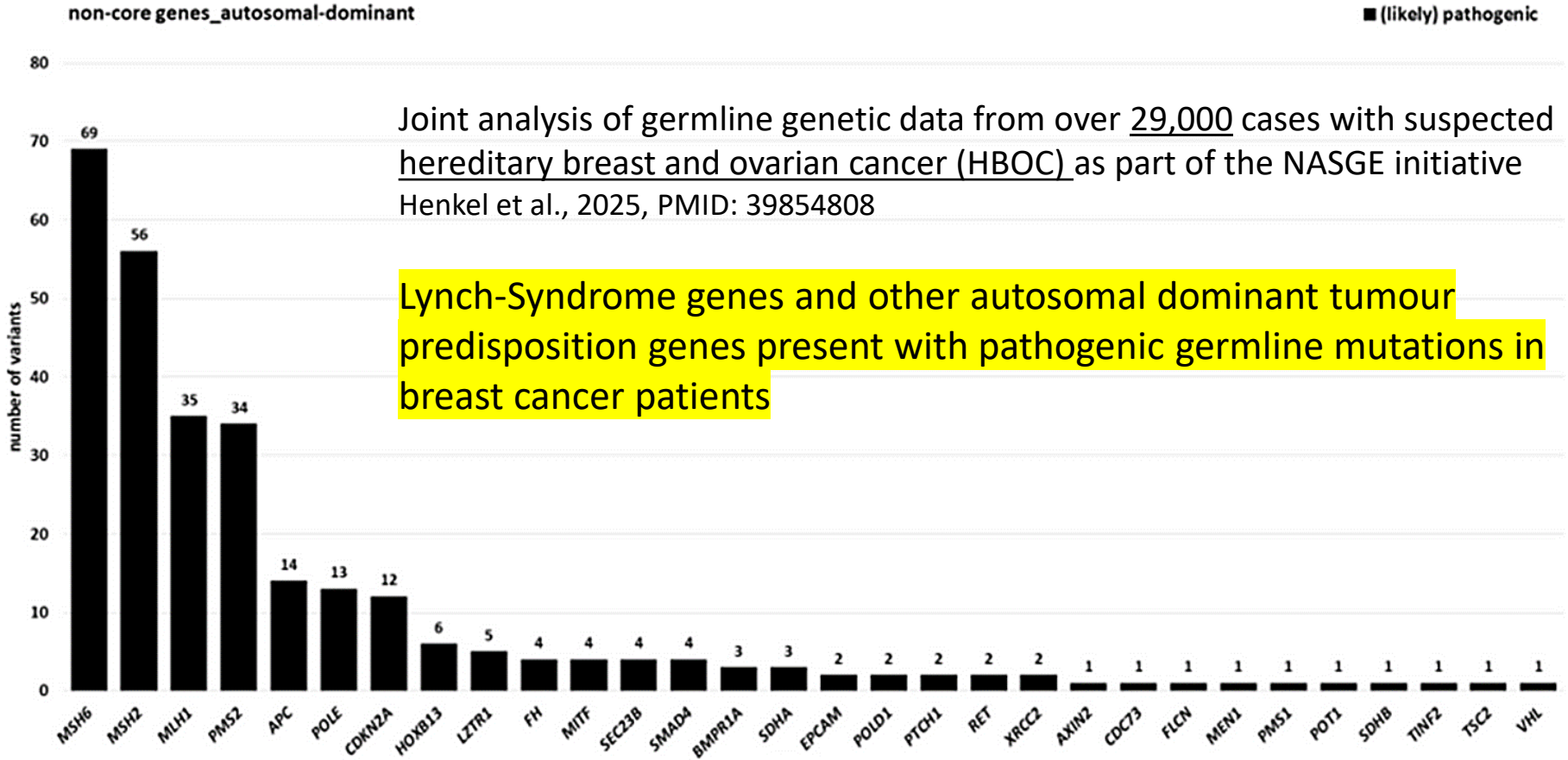

Joint analysis of germline genetic data from over 29,000 cases with suspected hereditary breast and ovarian cancer (HBOC) as part of the NASGE initiative

Henkel et al., 2025, PMID: 39854808

Lynch-Syndrome genes and other autosomal dominant tumour predisposition genes present with pathogenic germline mutations in breast cancer patients

Germline mutations – somatic diagnostics cases

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- Patients present with breast cancer
- All germline panel genes are always analysed in somatic diagnostics as part of the tumour-normal comparison workflow
- Patients/referring physicians do not always request familial predisposition testing, though patients with hereditary breast cancer can be part of the cohort

-> Such patients are more likely have “sporadic”/non-hereditary breast cancer

Germline mutations in somatic diagnostics cases

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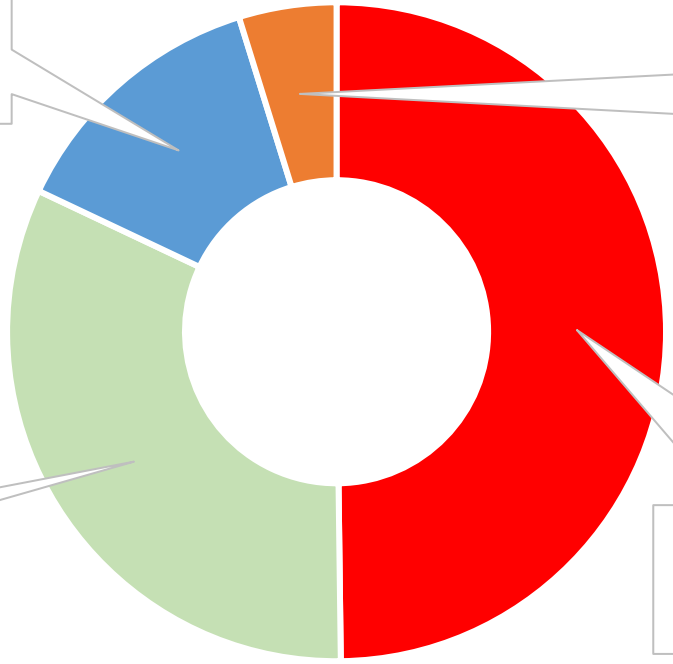
Somatic cases - distribution of pathogenic germline variants among gene groups

Other AD genes
2.56% diagnostic yield;
13.18% of all pathogenic variants

Lynch-Syndrome
0.93% diagnostic yield;
5% of all pathogenic variants



	Testing condition	
	Active tumor	Family history
Core Genes	9.67%	**11.23%**
Recessive genes	6.26%	3.74%
Other AD genes	**2.56%**	1.79%
Lynch-Syndrome	**0.93%**	0.3%

+ 3.49 % potential differential diagnosis!

Recessive genes
6.26 yield;
32% of all pathogenic variants

HBOC core genes
9.67% diagnostic yield;
50% of all pathogenic variants

Somatic diagnostics - Biomarkers

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- Somatic diagnostics covers the following additional Biomarkers
  - Homologous recombination deficiency (HRD) based on NGS data
  - Microsatellite instability (MSI) prediction and TMB calculation based on NGS data
  - Viral infection screening (HPV, EBV, CMV, MCV)
  - **RNAseq-based gene fusion analysis** (optional) + DNAseq-based breakpoint detection (default)

Somatic diagnostics - Biomarkers

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- HRD was detected in 44% of analysis
- TMB high (>10) was determined for 4.33% of breast cancer cases
- MSI (unstable) was determined for 0.17% of breast cancer cases

-> Therapeutic options are detected outside the classic HBOC gene spectrum

- No cases presented with a viral infection of the tumor tissue

Somatic diagnostics – gene fusions in breast cancer?

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- 392 RNAseq-based fusion analyses were performed for breast cancer patients using an LDT panel (>200 genes)
- 3.6% of all analyses yielded a potentially druggable gene fusion
- Oncogenic effect is mostly via activation of oncogenes, but inactivation of tumour suppressor genes is also observed
- Fusions are mostly unique events
- Fusions of unknown significance (VUS) are frequently detected (29% of analysed cases)

Druggable fusions	
first gene	second gene
NDUFB9	*ATRX*
ESR1	*ARMT1*
ESR1	*CCDC170*
ESR1	*MYO9A*
ESR1	*TBCE*
NSD3	*FGFR1*
AGAP1	*FGFR2*
FGFR2	*TMC3-AS1*
PVT1	*MYC*
NF1	*NF1*
BCL9	*NOTCH2*
ANKRD30A	*NRG1*
ZNF652	*NTRK3*
CCDC127	*TERT*

Somatic diagnostics

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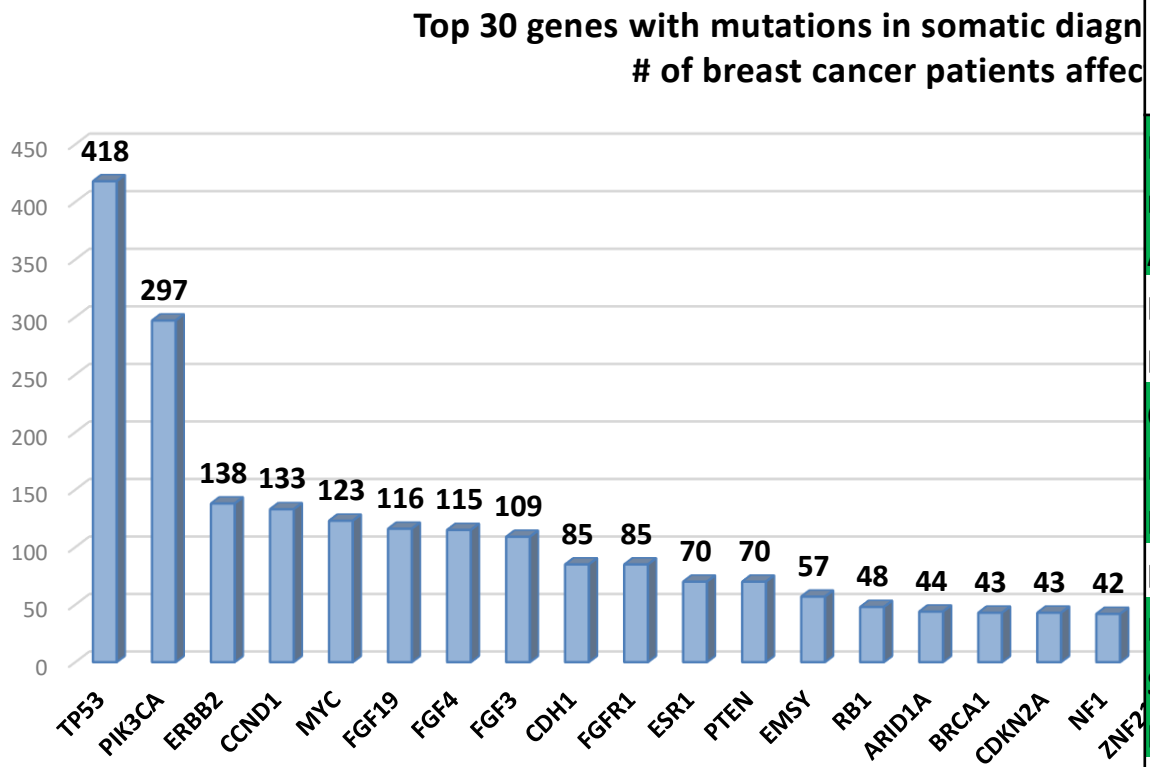

Drug classes indicated - TOP 30 genes
PARP inhibitor
mTOR inhibitor
AKT inhibitor
FGFR inhibitor
MEK inhibitor
CDK4/6 inhibitor
PI3K inhibitor
Immune checkpoint inhibitor
HDAC inhibitor
HER2 inhibitor / Antibody-drug conjugate
Selective estrogen receptor degrader (SERD)
Endocrine therapy
EZH2 inhibitor
EGFR inhibitor

Somatic diagnostics

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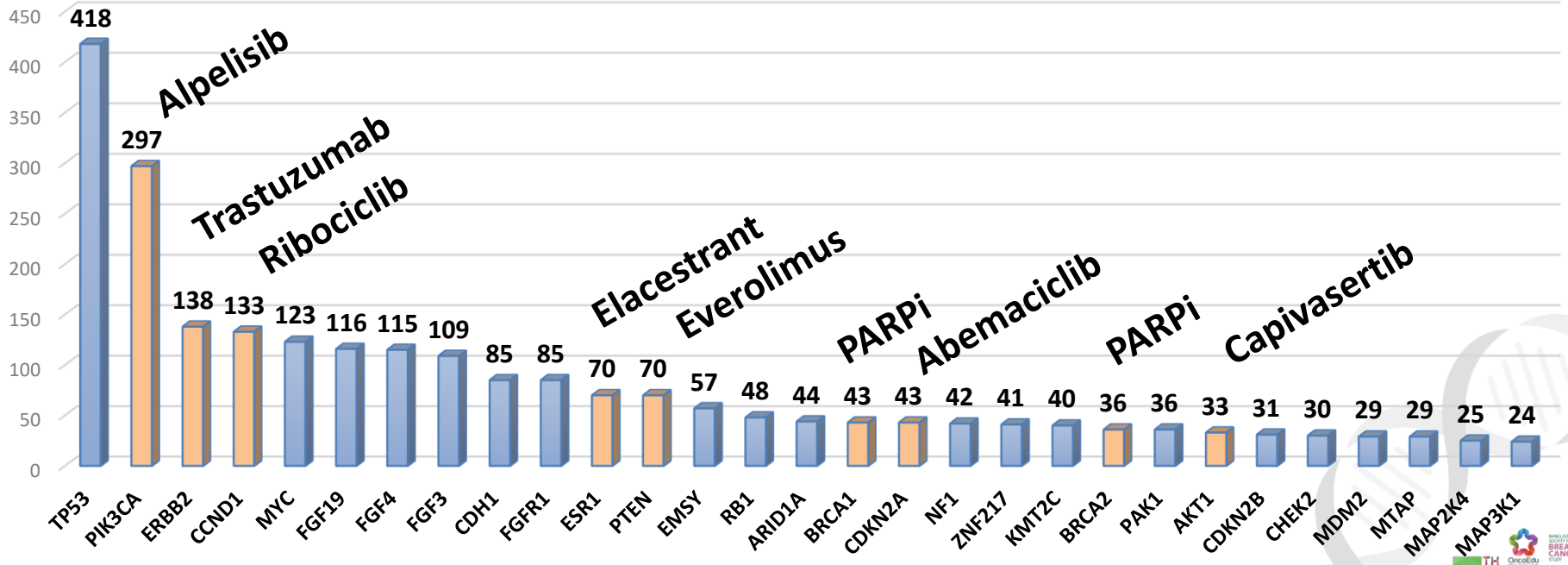
Top 30 genes with mutations identified via somatic diagnostics (SNV/CNV)
# of breast cancer patients affected - highlight: FDA/EMA approved drugs available



Conclusions – genetic diagnostics in breast cancer

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- **Choose comprehensive panels in germline testing**. It's not all in the core genes. For affected patients, always combine germline and somatic testing!
  - Always **choose tumour:normal comparison** to understand what really drives the cancer
  - This approach also allows a reliable calculation of biomarkers (e.g. TMB,…) based on NGS data
- For somatic diagnostics, **fusion detection** can lead to additional therapeutic options
- Selection of the best therapeutic option for a patient after somatic diagnostics does highly benefit from consulting a **molecular tumour board**

Thank you!

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