HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

DEUTSCHES KONSORTIUM
für familiären Brust- und Eierstockkrebs

unterstützt durch die Deutsche Krebshilfe

Genetische Prädisposition bei Patientinnen mit hohem Risiko für familiären Brust- und Eierstockkrebs

Dieter Niederacher
Zentrum für Familiären Brust- und Eierstockkrebs, Düsseldorf

Angelina Jolie's Aunt Dies of Breast Cancer

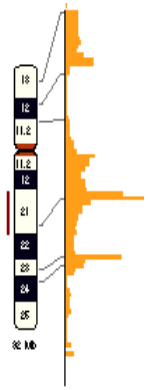
By JACKIE FIELDS AND JESSICA HERNDON

05/26/2013 at 06:10 PM EDT

1994

2013

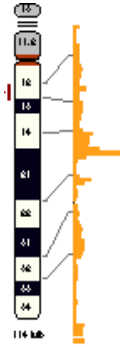
Entdeckung der BRCA Gene



Lokalisation der Genregionen

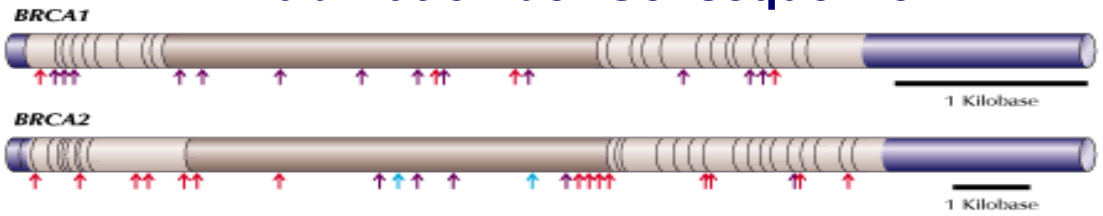
BRCA1: 17q21
Hall et al., 1990

BRCA2: 13q12-13
Wooster et al., 1994



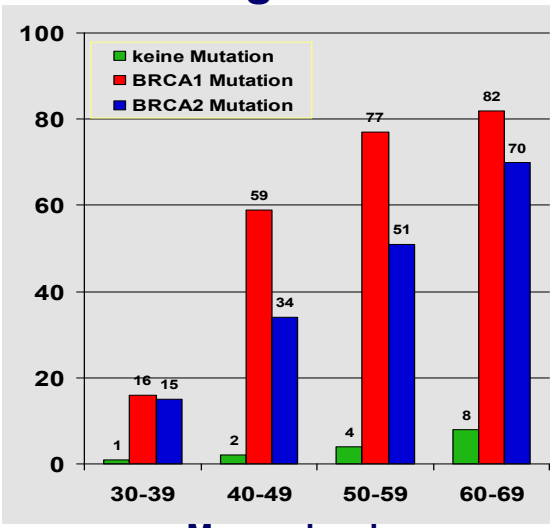
Publikation der Gensequenzen

1994

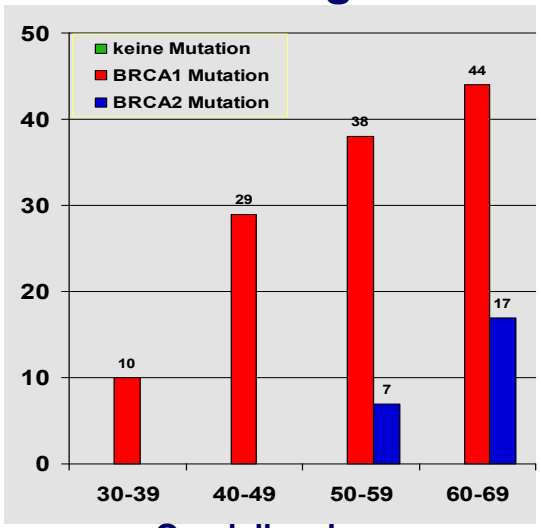


1996

Erkrankungsrisiken von BRCA1/2 Mutationsträgerinnen



Mammakarzinom



Ovarialkarzinom

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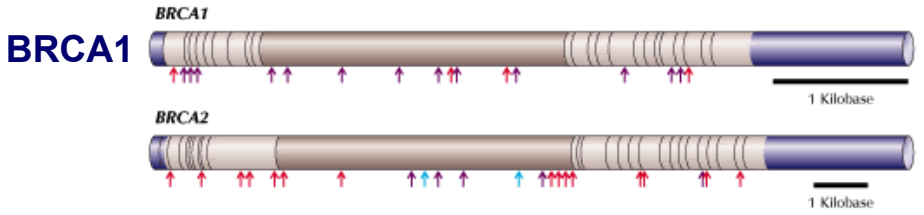
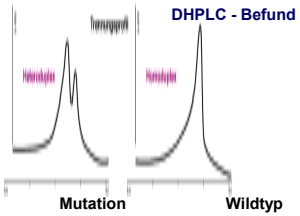
Multizentrische, interdisziplinäre Studie zum familiären Brust- und Eierstockkrebs (1997-2005)

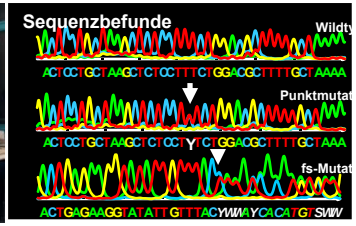
Individuelle, interdisziplinäre Beratung

- Gynäkologie/Geburtshilfe
- Humangenetik
- Psychosomatik/Psychotherapie
- prädiktive genetische Diagnostik



Implementierung der NGS-Technologie in der genetischen Diagnostik (multi-gene-panels)





Konventionelle Mutationsanalyse
DHPLC-Screening + DNA-Sequenzierung

„Next-Generation-Sequencing“
(NGS-) Mutationsanalyse

Genetische Analyse Stand 2014

„4 gene set“

BRCA1
BRCA2
RAD51C
CHEK2

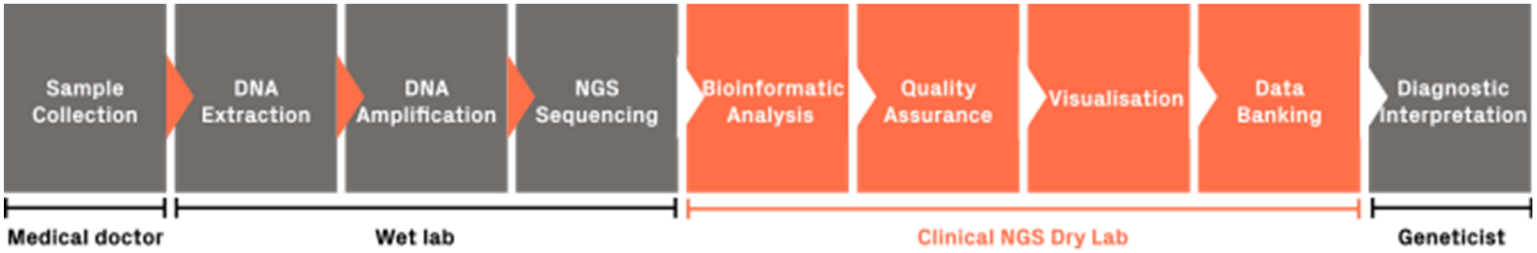
TruRisk® gene panel (34 genes) of the German Consortium

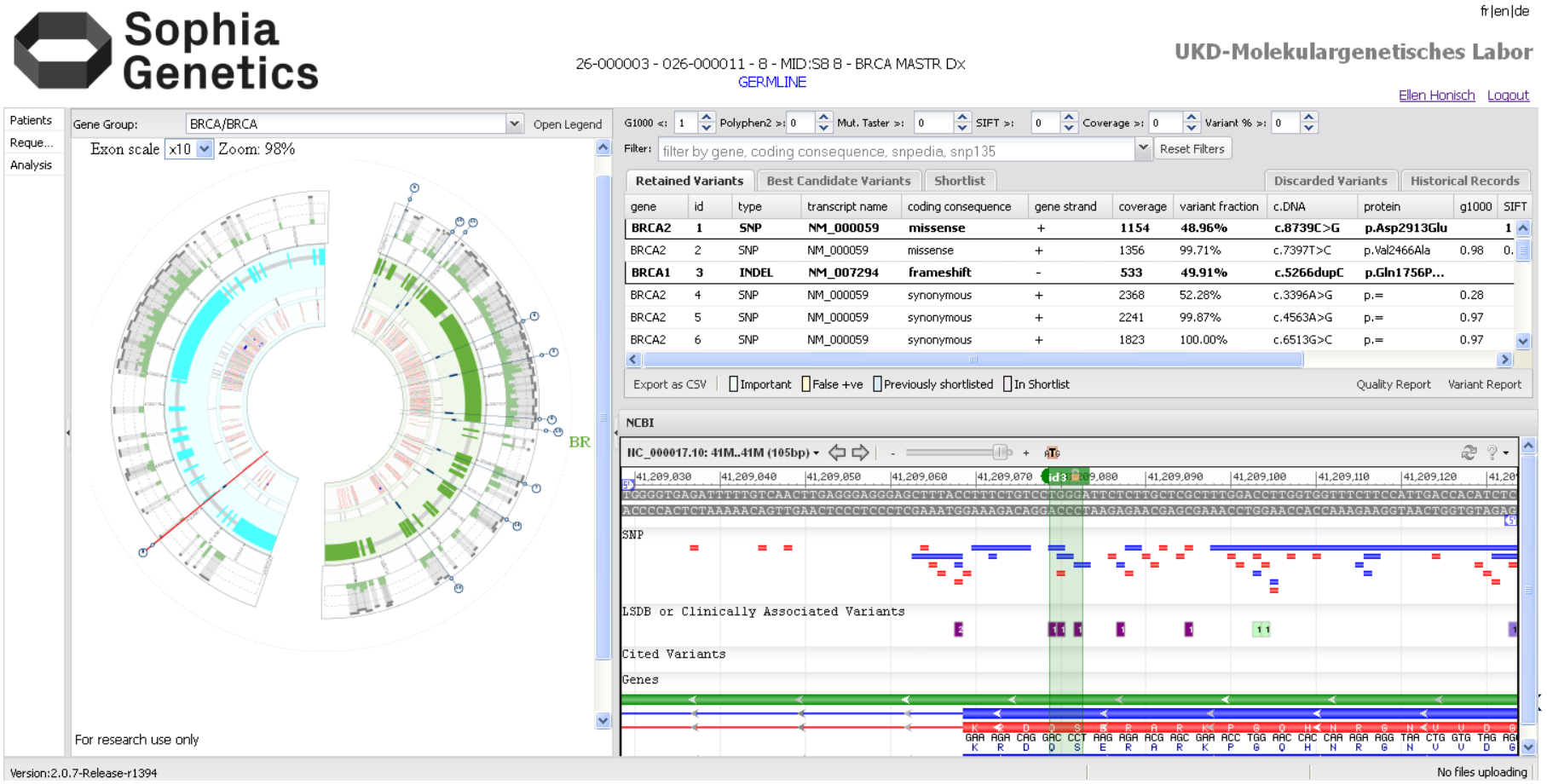
comprehensive analysis of all known risk and candidate genes

Routine ab 1.10.2015

ATM core gene	BRCA1 core gene	BRCA2 core gene	CDH1 core gene	CHEK2 core gene	NBN core gene	PALB2 core gene	RAD51C core gene
RAD51D core gene	TP53 core gene	MLH1 Lynch syndrome	MSH2 Lynch syndrome	MSH6 Lynch syndrome	PMS2 Lynch syndrome	ENIGMA gene	ENIGMA gene
ENIGMA gene	ENIGMA gene	ENIGMA gene	ENIGMA gene	ENIGMA gene	ENIGMA gene	ENIGMA gene	ENIGMA gene
ENIGMA gene	ENIGMA gene	candidate Konsortium	candidate Konsortium	candidate Konsortium	candidate Konsortium	candidate Konsortium	candidate Konsortium
candidate Konsortium	candidate Konsortium						

Bioinformatische Datenanalyse

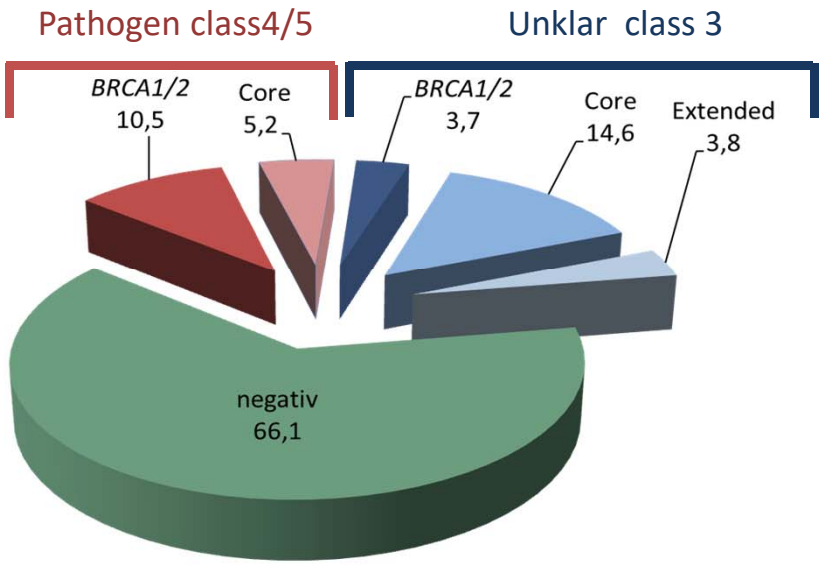




Mutationsfrequenzen HBOC Index-Patienten [%]

Pathogenitätsbewertung von Sequenzvarianten ???

Klinische Handlungsoptionen/ -empfehlungen



The Oncologist®

Clinical Genetics and Genetic Counseling

BRCA1/2 Sequence Variants of Uncertain Significance: A Primer for Providers to Assist in Discussions and in Medical Management

Noralane M. Lindor,[a] David E. Goldgar,[b] Sean V. Tavtigian,[c] Sharon E. Plon,[d] Fergus J. Couch[e]

Table 2. Proposed classification for DNA sequence variants and correlation of clinical recommendation with probability that any given alteration is deleterious

DNA alteration class	Definition	Probability of being deleterious	Clinical testing	Surveillance recommendations
5	Definitely pathogenic	>0.99	Test at-risk relatives for the variant	Full high-risk surveillance
4	Likely pathogenic	0.95–0.99	Test at-risk relatives for the variant	Full high-risk surveillance
3	Uncertain	0.05–0.949	Do not use as predictive testing in at-risk relatives	Counsel based on family history and other risk factors
2	Likely not pathogenic	0.001–0.049	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected
1	Not pathogenic	<0.001	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected

Table adapted from Plon et al. 2008 [8]. Note that for most variants, a quantitative probability is not yet available, as insufficient lines of evidence exist to generate the probability.

Laboratory reference number

Institution: *EMQN Genetic test*
Physician: *Consultant Clinical Geneticist*
Address: *Manchester*

Molecular diagnosis of familial breast/ovarian Cancer

BRCA1 Mutation analysis

Name:	**ONETH**		Sample N#:	17OA000133
First name:	**MARY**		Sample type:	DNA
Date of birth:	08/05/1969	Sex: F	Sampling date:	Unknown
Family N#:			Reception date:	11/01/2017
Internal ref. N#:	661701039799		*External ref. N#:*	*Batch 16011804*

Clinical background: Proband with breast cancer and family history of breast cancer.

Molecular analysis:

Sanger sequencing analysis of targeted regionc.1900_c.2200 with the numbering starting at the A of the ATG initiation codon of the *BRCA1* gene. Sanger sequencing with a dye terminator cycle sequencing kit using an automatic DNA sequencer ABI 3730 (sensibility>95%). CNV detection: Multiplex Ligation Dependent Probe Amplification (MLPA, MRC Holland) sur ABI 3730 kit MLPA BRCA1 P002-D1, kit MLPA BRCA2 P045-C1 (Sensibilité>95%).
Reference BRCA1: LRG_292t1

Molecular analysis result:

Identification of a heterozygous variant c.2083G>T, p.Asp695Tyr in *BRCA1* gene. This rare missense variant is described in the French database as **neutral variant** (class 1). None other significant variant was identified including gene rearrangement.

Conclusion:

According to technical limitations, **no mutation responsible for hereditary predisposition to breast/ovary cancer was identified.** In front of the family history and the negative test result for *BRCA1* and *BRCA2* mutations (previously done), another affected family member should be tested (her sister who developped breast carcinoma at 35 years of age), as Mary Oneth could be a phenocopy. Another genes involved in hereditary predisposition of breast cancer (*PALB2*) could also be tested.
A heritable predisposition to breast cancer cannot be excluded for Mary Oneth and she should follow a medical surveillance for her and her relatives according to familial history of breast cancer.

Biologist 1 x Biologist 2 x

Date of report: 17/03/2017

GENeALYSE – Standardisierte Dokumentation für Gentests/ Übermittlung von Biomarker- und Genomanalysedaten

Fazit, Ziele und Projektplan

- im Projekt GENeALYSE soll eine standardisierte und interoperable Grundlage für die Befundung erarbeitet werden
- Ziel ist die Bereitstellung eines Implementierungsleitfadens zur Standardisierung der Ergebnisübermittlung

Vorgehen

- Analyse der IST Situation bei Expertentreffen
  - Klinische Fragestellung und Anforderung
  - Übermittlung von Anforderung und Probenmaterial
  - Probeneingang
  - Befunderhebung
  - Befunderstellung und -Übermittlung
- Erstellung einer SOLL-Konzeption
  - Diskussion und Finalisierung in gemeinsamen Expertentreffen

UKD Universitätsklinikum Düsseldorf
HEINRICH HEINE UNIVERSITÄT DÜSSELDORF
Klinik für Frauenheilkunde und Geburtshilfe

Hochschule Niederrhein
University of Applied Sciences

UNIKLINIK KÖLN

Herausforderungen und neue Ansätze zur personalisierten Krebstherapie

Herausforderungen

- **Anpassung der Therapie an die individuelle Krebserkrankung** für effiziente und sichere Behandlungsoptionen
- **Limitiertes Tumormaterial**
- **Limitierte Zeit** für Arzt und Patienten bis zur nächsten Therapieentscheidung
- **Big Data:** Sinnvolle Auswertung und klinische Interpretation von großen Datenmengen an genetischer Information

Neue Analyseansätze

Molekulare Tumor-Profilierung mit NGS-Technologie mit Panel und Whole Exome

Computergestützte Tumor Analyse & Interpretation

Vielen Dank
Für Ihre Aufmerksamkeit!