Hereditary breast cancer beyond BRCA1/2

Cornelia Leo

Brustzentrum, Kantonsspital Baden

6th Introductory Course of Genetic Counseling in Oncology,
Fachhochschule St.Gallen, 8th and 9th of March 2019

Agenda

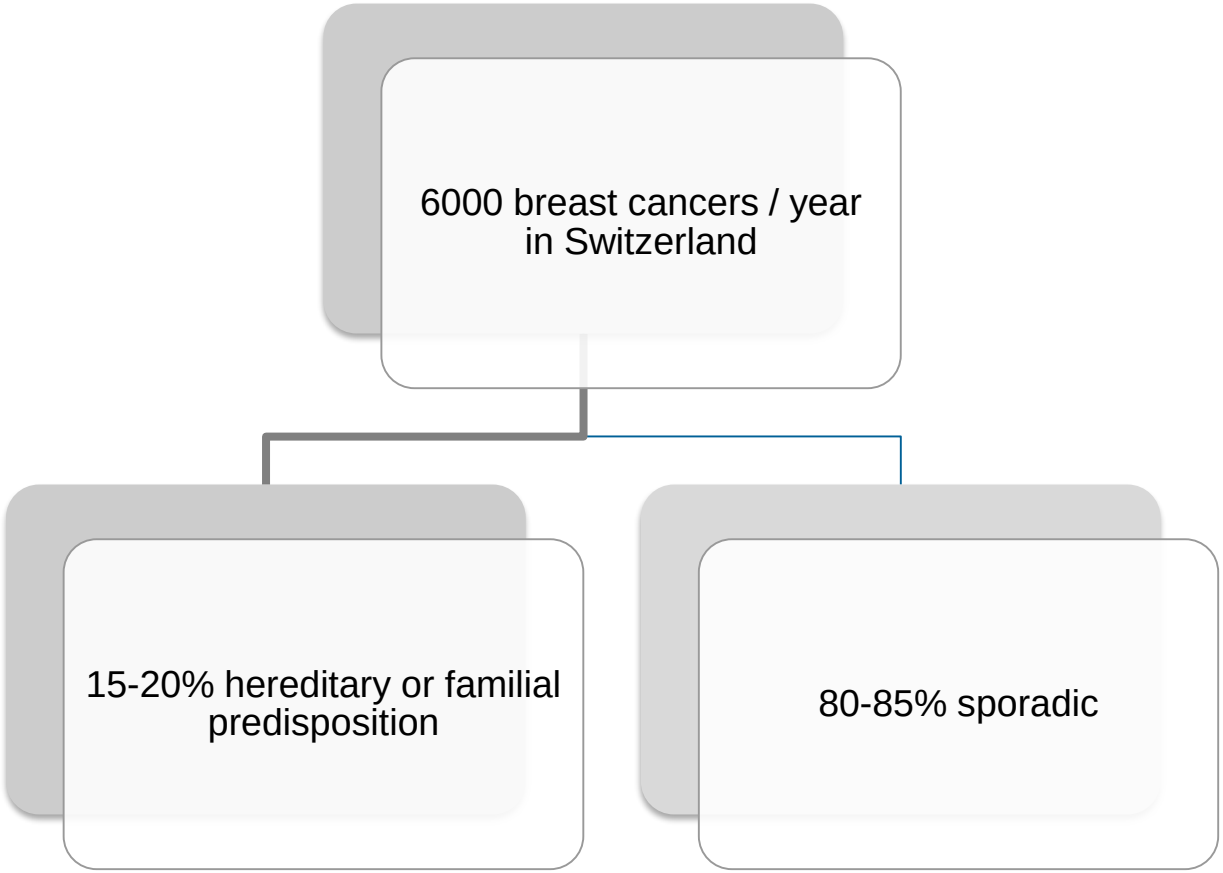
1) Introduction

2) Breast cancer genes

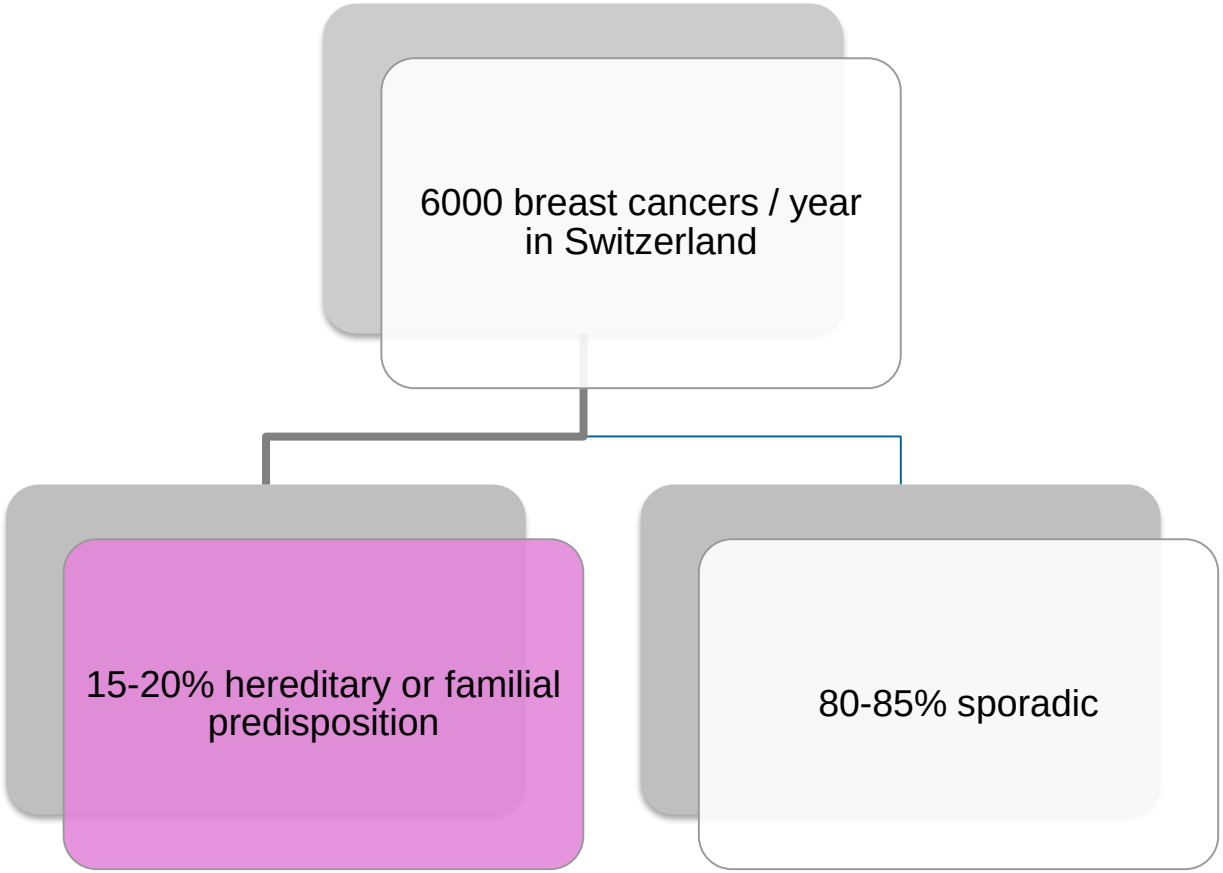
3) Syndromes (Li-Fraumeni, Cowden, Peutz-Jeghers, hereditary diffuse gastric cancer syndrome)

4) Management of high risk women

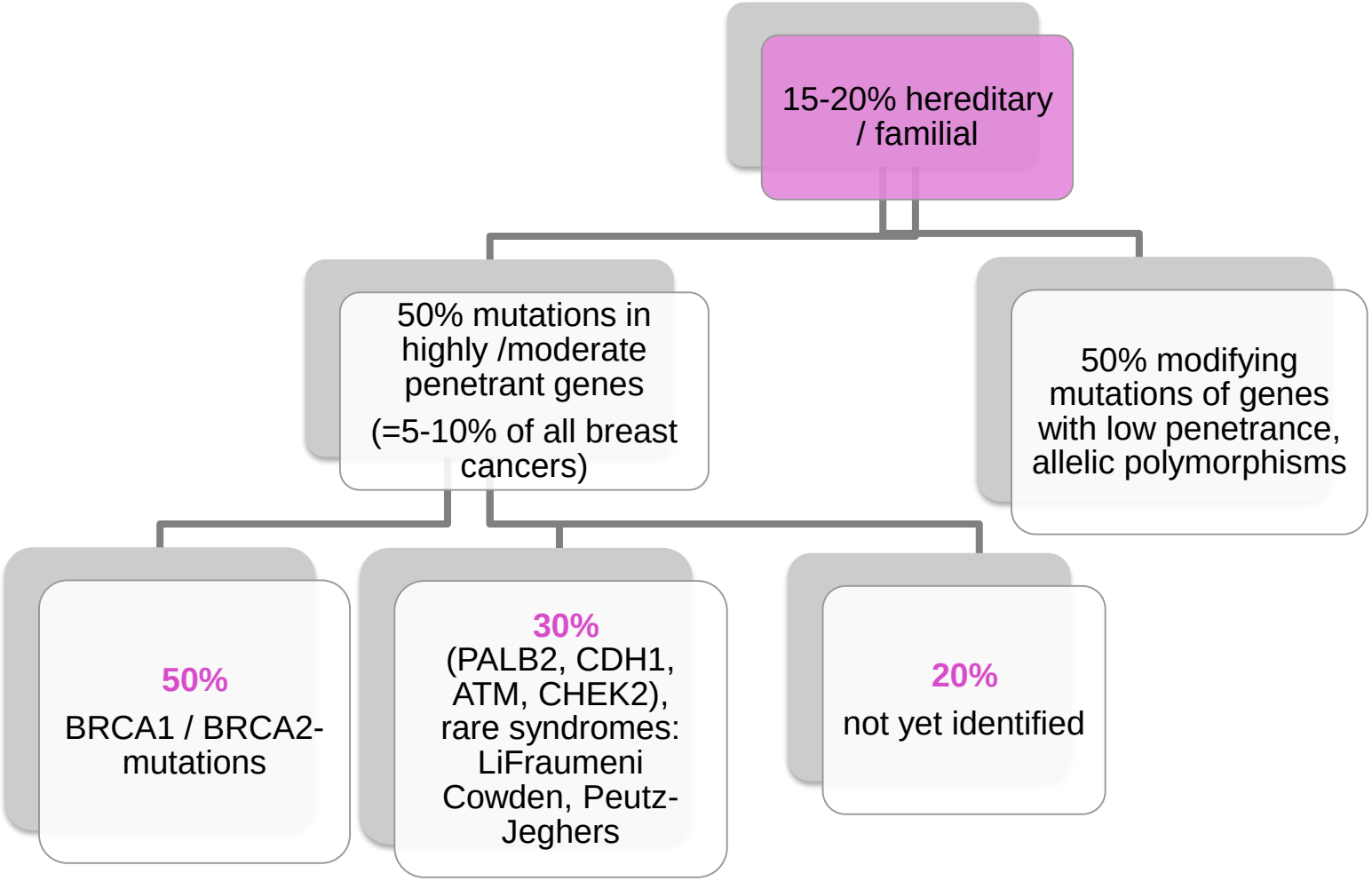
Breast cancer - numbers



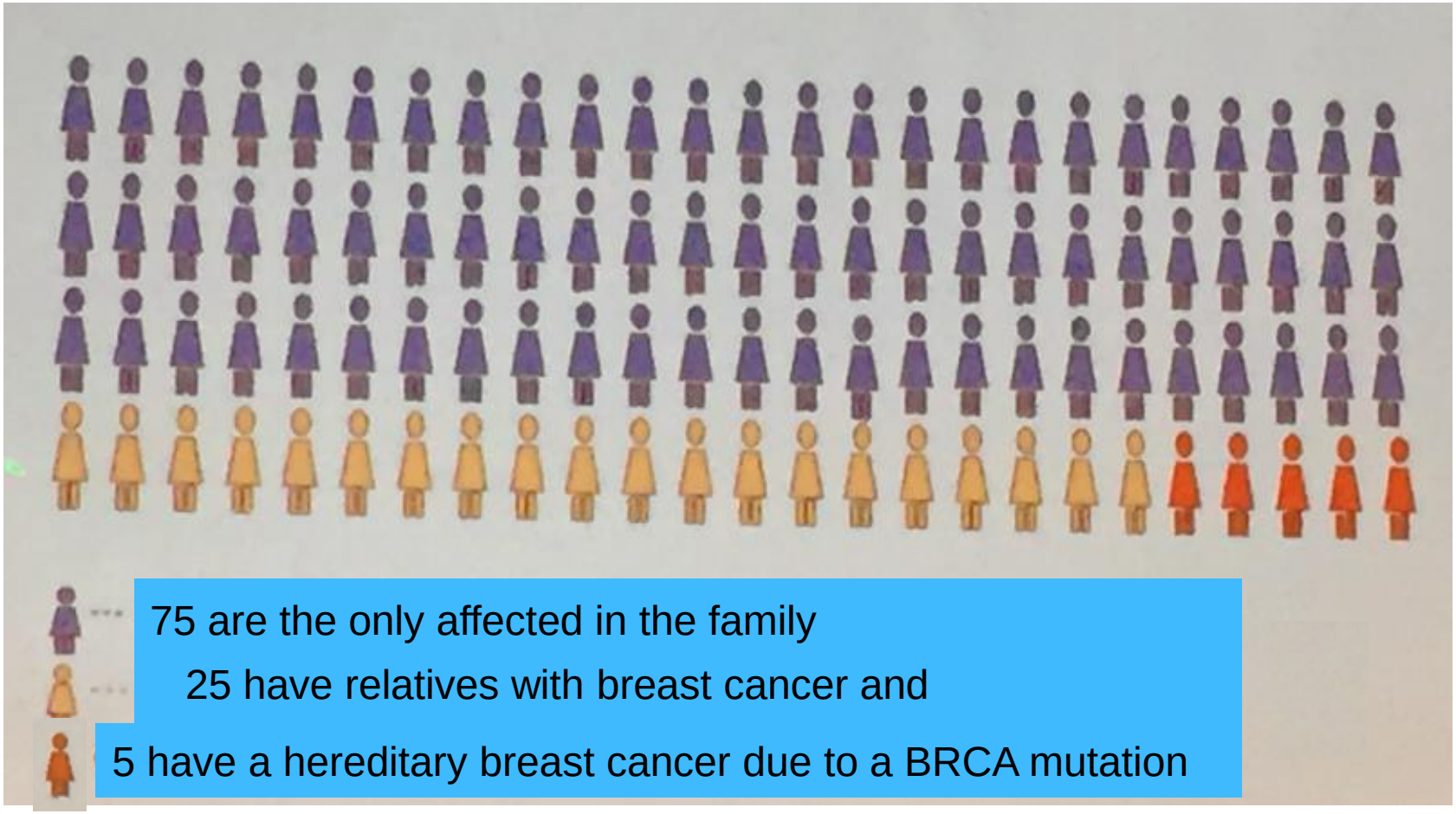
Breast cancer - numbers



Breast cancer - numbers



Of 100 women diagnosed with breast cancer



Agenda

1) Introduction

2) Breast cancer genes

3) Syndromes (Li-Fraumeni-, Cowden-, Peutz-Jeghers-, hereditary diffuse gastric cancer syndrome)

4) Management of high risk patients

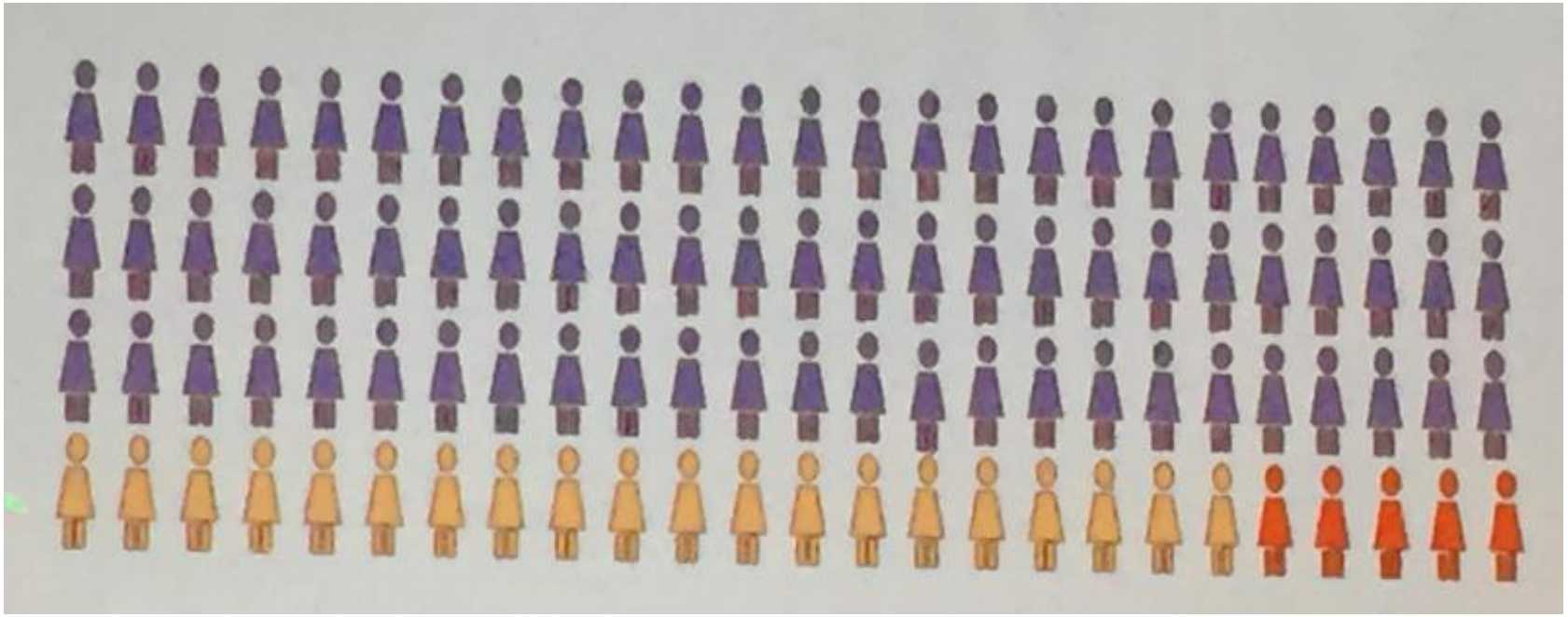
Highly penetrant breast cancer genes: increase of risk 5-20fold

BRCA1 / BRCA2	• HBOC Syndrome
TP53	• Li-Fraumeni syndrome
PTEN	• Cowden syndrome
STK11 / LKB1	• Peutz-Jeghers syndrome
CDH1	• Diffuse Gastric Cancer Syndrom
PALB2	

Other breast cancer genes

Moderately penetrant breast cancer genes: Risk 1.5 – 5fold	**Low risk genes: Risk 0.7 – 1.5fold**
ATM CHEK2 NF NBN	FGFR2, TOX3, MAP3K1, CAMK1D, SNRPB, FAM84B/c-MYC, COX11, LSP1, CASP8, ESR1, ANKLE1, MERIT40 Etc.

Of 100 women diagnosed with breast cancer



plus low risk genes
plus „familial predisposition“

TP53, PTEN,
STK11, CDH,
PALB2, ATM,
CHEK2, NBN, NF1 ...

BRCA1/2

Kantonsspital Baden
KSB

Agenda

1) Introduction

2) Breast cancer genes

3) Syndromes (Li-Fraumeni, Cowden, Peutz-Jeghers, hereditary diffuse gastric cancer syndrome)

4) Management of high risk patients

Li-Fraumeni syndrome

Mutations or deletions in TP53 → frequency: 1 / 20 000

Typical LFS associated cancers:

- Bone- and soft tissue sarcoma
- Breast cancer
- Brain tumors
- Adrenocortical carcinoma

• Monogenic autosomal dominant inheritance

• offspring has 50% risk of inheriting the gene defect

Li-Fraumeni syndrome

Other LFS associated tumor entities

- Colorectal cancer
- Endometrial cancer, germ cell tumors, ovarian cancer
- Malignant phylloid tumors
- Esophageal cancer
- Leucemia, lymphoma
- Lung cancer
- Melanoma
- Pancreatic cancer
- Prostate cancer
- Gastric cancer
- Thyroid cancer
- Willms tumor

Li-Fraumeni syndrome

Risk for LFS associated tumors:

- 50% to age 30
- 90% to age 60

Risk for 2nd cancer: up to 57%

Risk for tertiary cancers: up to 38%

Li-Fraumeni syndrome

criteria for LFS:

Individual diagnosed age < 45 y with sarcoma **and**

First degree relative diagnosed age < 45 y with cancer **and**

First or 2nd degree relative diagnosed age < 45 y with cancer or sarcoma at any age

In 70% of LFS families a TP53-Mutation is detected

Li-Fraumeni syndrome: criteria for TP53 testing

1) Individuals with classic LFS criteria

2) Individuals with Chompret criteria:

- Typical LFS associated tumors < 46y **plus** first/second degree relative with tumor from LFS spectrum <56y or multiple tumors at any age

or

- Individual with multiple tumors, 2 of which belong to typical LFS spectrum and first tumor < 46y

or

- ACC or choroid plexus carcinoma (rare brain tumor) or rhabdomyosarcoma (embryonal anaplastic subtype) at any age of onset regardless of family history

or

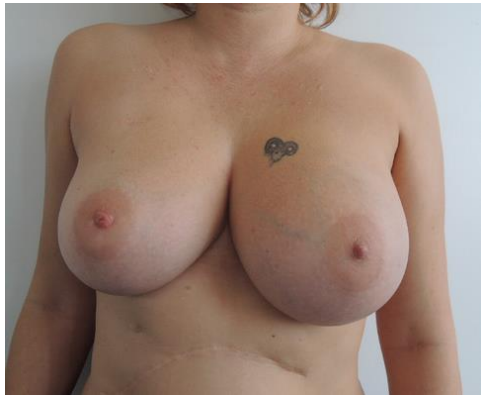
- Women with breast cancer ≤ 30 y and negative BRCA1/BRCA2 testing

Aus: NCCN guidelines Version 2018

Li-Fraumeni syndrome: case example

34 y/o patient with increase in size of the left breast

Tru cut biopsy: Malignant Phylloid tumor



History:

At 20y: embryonal liver sarcoma (in complete remission)

Uneventful family history

Staging at presentation:

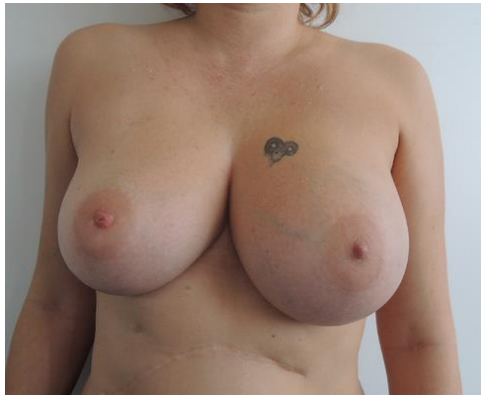
Mammography: invasive breast cancer right side

CT Thorax: pulmonary mass: adenocarcinoma of the lung

Li-Fraumeni syndrome: case example

34 y/o patient with increase in size of the left breast

Tru cut biopsy: Malignant Phylloid tumor



History:

At 20y: embryonal liver sarcoma (in complete remission)

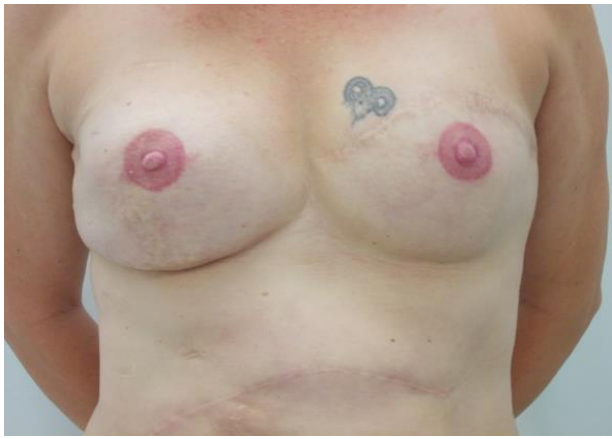
Uneventful family history

Staging at presentation:

Mammography: invasive breast cancer right side

CT Thorax: pulmonary mass: adenocarcinoma of the lung

Li-Fraumeni syndrome: case example



Therapy:

- Partial liver resection at age 20y plus adjuvant chemotherapy

- Bilateral mastectomy and SLN 2013 (age 34y)

- Partial lung resection right 2013 (age 34y)

- Delayed reconstruction with expander / implant 2013/2014

- Tamoxifen

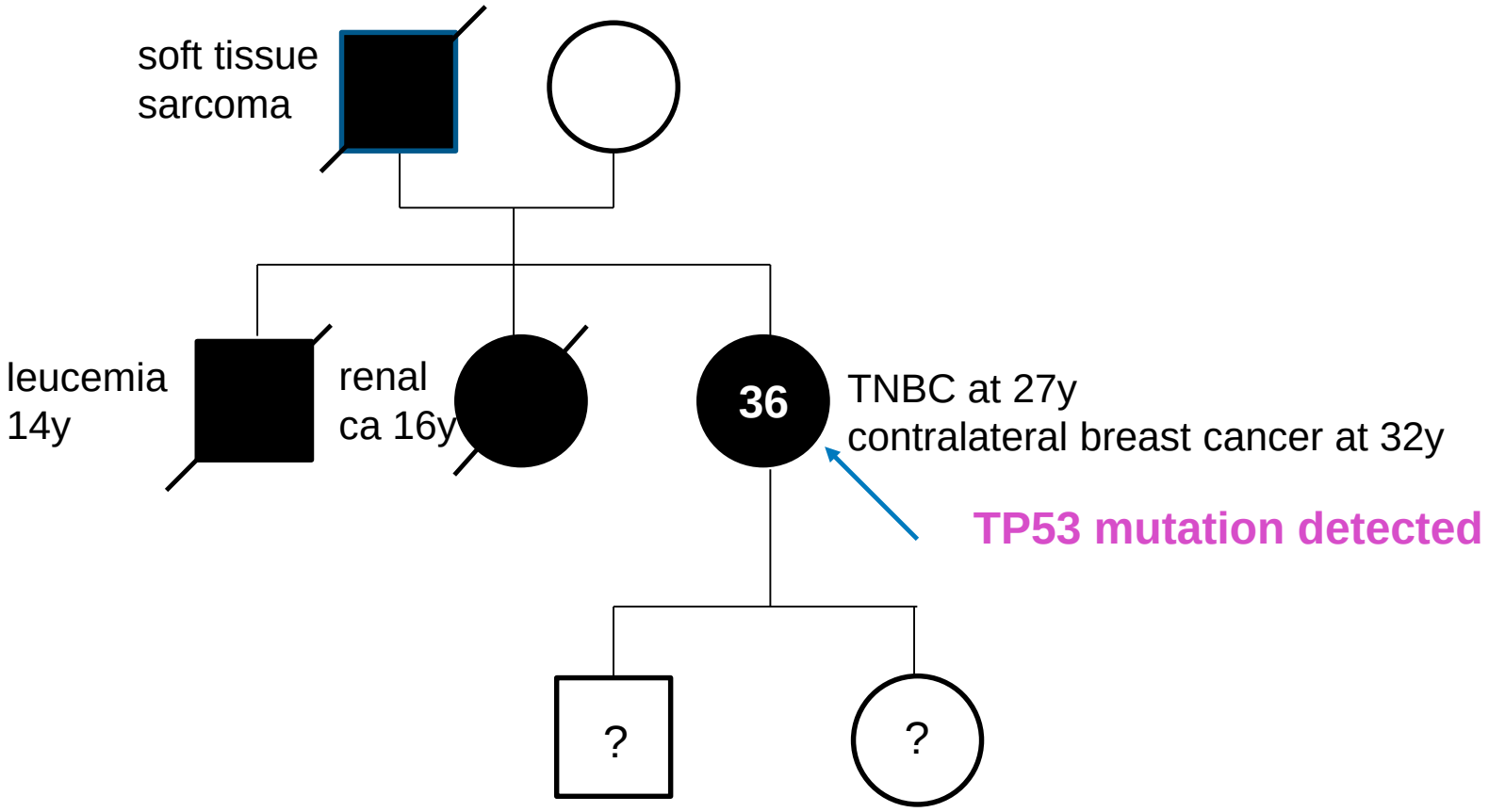
Li-Fraumeni syndrome: case example

- fulfills Chompret criteria for LFS
- had genetic counseling
- Decides against TP53 testing

<u>Follow-up:</u>

- annual breast MRI
- annual gynaecological exam with TVS
- PET-CT (better MR??)
- Last check-up: colonoscopy with removal of multiple benign polyps

Li-Fraumeni syndrome: 2nd case example



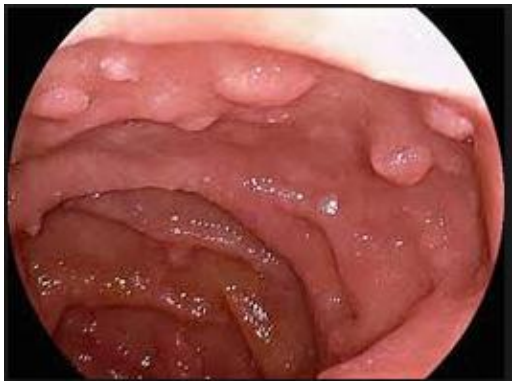
Kantonsspital Baden
KSB

Li-Fraumeni syndrome: 2nd case example

Follow-up:

- Annual whole body MRI
- Annual gynaecological exam with TVS
- Annual dermatology check-up
- Colonoscopy every 2-5 years
- Children of patient are currently in evaluation

Cowden syndrome (PTEN hamartoma syndrome, PHS)



- Mutations or deletions in **PTEN** →

  frequency: 1 / 200 000

Typical for Cowden syndrome:

- Benign hamartomatous polyps of skin and mucous membranes,

  gastrointestinal tract, thyroid and breast

- Macrocephaly can occur

- Monogenic autosomal dominant inheritance
- offspring has 50% risk of inheriting the gene defect

Cowden syndrome (PTEN hamartoma syndrome, PHS)

Women with PTEN mutation:

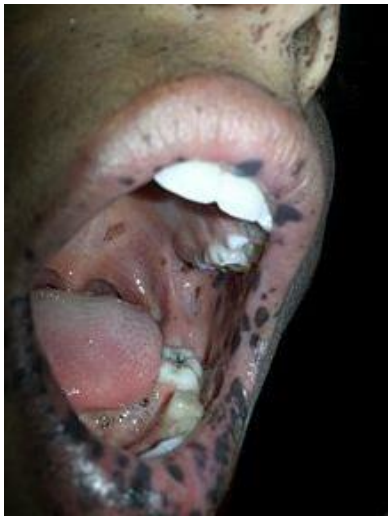
– Lifetime risk for breast cancer 25-50%
– Lifetime risk for endometrial cancer 6-10%
– Lifetime risk for thyroid cancer 10%

Men with PTEN mutation:

– Lifetime risk for thyroid cancer 10%
– Increased breast cancer risk

In addition, increased risk for renal cell carcinoma

Peutz-Jeghers syndrome



Quelle: Wikipedia

Mutations or deletions in **STK11** →

frequency: 1 / 25 000 to 1 / 280 000

Typical for Peutz-Jeghers syndrome:

- Gastrointestinal polyposis with characteristic melanotic spots of skin and mucous membranes
  - Benign hamartomatous polyps in gastrointestinal tract (> 100)
  - Melanotic dark spots of skin and mucous membranes

- Monogenic autosomal dominant inheritance
- offspring has 50% risk of inheriting the gene defect

Peutz-Jeghers syndrome

85% lifetime risk for cancer

- Risk for gastrointestinal cancer: 57%
- Risk for colorectal cancer: 39%
- Also associated are renal, lung and thyroid cancer

Women with STK11 mutation:

- Breast cancer risk 44 - 50%
- Risk for ovarian cancer and granulosa cell tumors 18 - 21%
- fallopian tube carcinoma, cervical carcinoma

Men with STK11 mutation:

- Benign Sertoli tumors of testis
- Increased prostate and breast cancer risk

Hereditary diffuse gastric cancer syndrom

Mutations or deletions in **CDH1** →

frequency: not known / rare

- Lifetime risk for diffuse gastric cancer:
  - 83% for women
  - 70-80% for men

- Lifetime risk for lobular breast cancer: 39 - 52%

- Monogenic autosomal dominant inheritance
- offspring has 50% risk of inheriting the gene defect

Hereditary diffuse gastric cancer syndrom

Criteria for CDH1 testing:

- Families with 2 or more gastric cancers, at least one of which of diffuse subtype, one < 50yrs
- 1 individual with diffuse gastric cancer <40y
- Personal or family history of diffuse gastric cancer as well as lobular breast cancer, at least one individual with diagnosis <50y

Agenda

1) Introduction

2) Breast cancer genes

3) Syndromes (Li-Fraumeni-, Cowden-, Peutz-Jeghers-, hereditary diffuse gastric cancer syndrome)

4) Management of high risk women

Intensified high risk screening

(Self) palpation starting at (20-) 25y every 6-12 months

Annual mammography starting age 30y

Annual MRI

Starting at 20y (LFS)

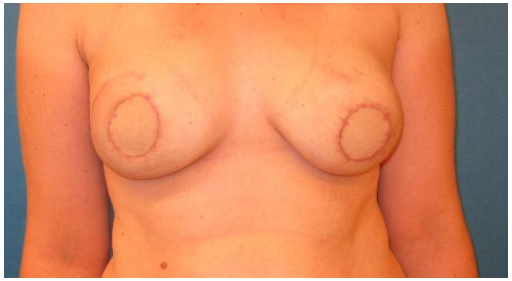
Starting at 25y (HBOC)

Starting at 30y (Cowden)

According to NCCN Guidelines

Kantonsspital Baden KSB

Risk-reducing mastectomy



- no or insufficient data for benefit of risk-reducing mastectomy outside HBOC syndrome
- therefore, no recommendation

- Individual counseling must take into account the kind of mutation and the family history

Li-Fraumeni syndrome: Management

- Palpation of the breast every 6-12 months, starting age 20-25y
- Annual breast MRI from 20y.
- (starting age 30y. additional annual MG (NCCN); Switzerland: BAG → no MG)
- Discussion regarding risk-reducing mastectomy (no data, benefit unclear)

Other cancer risks

- Information concerning limitations of screening for other LFS cancers
- Annual check-up, including dermatologist
- no therapeutic radiation therapy, if possible
- Discuss coloscopy every 2-5 years starting age 25y.
- Annual whole body MRI (incl. brain), try to avoid diagnostic radiation

Cowden syndrome: Management

Breast cancer

- Clinical breast exam every 6-12 months, starting at 20-25y.
- Annual breast MRI and MG starting at 30y
- No data concerning risk-reducing mastectomy

Endometrial cancer

- Counseling regarding abnormal symptoms (vaginal bleeding!)
- Consider annual endometrial biopsy and/ or TVS starting at 30-35y.
- Consider hysterectomy after completion of family planning (no data!)

Other 

- Annual physical examination starting at age 18y., incl. Thyroid exam
- Annual sonography of thyroid
- Colonoscopy every 5 years from age 35y.

- Consider renal sonography 40y every 1-2 years

Kantonsspital Baden KSB

Recommendations based on detected gene defect

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.		
BARD1	**Potential increase in breast cancer risk, with insufficient evidence for management recommendations**	**Unknown or insufficient evidence for ovarian cancer risk**	N/A
BRCA1	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	Prostate cancer • See *BRCA* Pathogenic Variant-Positive Management
BRCA2	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	Pancreas, Prostate, Melanoma • See *BRCA* Pathogenic Variant-Positive Management
BRIP1	**Unknown or insufficient evidence**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
CDH1	**Increased risk of lobular breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	Diffuse gastric cancer • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer

NCCN Guidelines Version 3.2019
Genetic/Familial High-Risk Assessment: Breast and Ovarian

Kantonsspital Baden
KSB

Recommendations based on detected gene defect

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CHEK2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		
MSH2, MLH1, MSH6, PMS2, EPCAM	**Unknown or insufficient evidence for breast cancer risk[g]** • Manage based on family history	**Increased risk of ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
NBN	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating pathogenic/likely pathogenic variant. Although risks for other pathogenic/likely pathogenic variants have not been established it is prudent to manage patients with other truncating pathogenic/likely pathogenic variants similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	• Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

Recommendations based on detected gene defect

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

The inclusion of a gene on this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management
RAD51C	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
TP53	**Increased risk of breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	See Li-Fraumeni Syndrome Management

Referenzdokument des Bundesamts für Gesundheit (BAG)

Alter	Brustkrebsrisiko-Kategorien					
	Risiko ***mässig ehöht***	Risiko ***stark erhöht***				
	17 – 29% Lebens-zeitrisiko*	≥30 % Lebenszeit-risiko*	>30% Wahrschein-lichkeit einer BRCA-Mutation*	BRCA1/2-Mutation	>30% Wahrschein-lichkeit einer p53-Mutation*	p53-Mutation
20 - 29	-	-	-	-	MRI jährlich	MRI jährlich
30 - 39	-	Jährliche Mammo-grafie erwägen	MRI jährlich, Jährliche Mammo-grafie erwägen	MRI jährlich, Jährliche Mammo-grafie erwägen	MRI jährlich	MRI jährlich
40 - 49	Mammografie jähr-lich	Mammografie jähr-lich	Mammografie + MRI jährlich	Mammografie + MRI jährlich	MRI jährlich	MRI jährlich
50 - 59	Jährliche Mammo-grafie erwägen	Mammografie jähr-lich	Mammografie jähr-lich, MRI nur bei hoher Brustdichte	Mammografie jähr-lich, MRI nur bei hoher Brustdichte	Mammografie jähr-lich, MRI nur bei hoher Brustdichte	Jährliches MRI er-wägen
60 – 69	Mammografie alle 2 Jahre	Mammografie alle 2 Jahre	Mammografie alle 2 Jahre**	Jährliche Mammo-grafie	Mammografie alle 2 Jahre***	-
70+	Mammografie alle 2 Jahre	Mammografie alle 2 Jahre	Mammografie alle 2 Jahre**	Mammografie alle 2 Jahre	Mammografie alle 2 Jahre***	-

Referenzdokument „Überwachungsprotokoll“
zu Artikel 12d Absatz 1d der Krankenpflege-Leistungsverordnung (KLV) in Anlehnung an NICE Clinical Guideline 164 vom Juni 2013 - Stand 02/2015

Take home message

- Occurence of other typical tumors/ cancers in the family

  → **think of syndromes beyond BRCA**

- Genetic counseling and genetic testing

- In case of detection of mutation or high risk constellation even without mutation

  suggest **high risk screening**

- Benefit of risk-reducing surgery only shown for HBOC

- **Individual discussion of risk-reducing surgeries** in individuals with other gene

  defects (balance risks and unclear potential benefit)

Thank you for your attention!