Genetics and Genomics

A view from daily practice in oncology today and tomorrow

Swiss Re Expert Forum on Genomic Medicine
22 / 23 October 2018
Rüschlikon/Zürich
Conflict of Interests

- My institution / myself receive honoraria and contributions from:
  - Amgen, AstraZeneca, Eli Lilly, Genomic Health, Pfizer, Swiss Government (SIPH)
- I own stock of Novartis and Roche
- The Swiss Group for Clinical Cancer Research SAKK receives contributions and research support from > 30 companies, NGOs and the Swiss Government (SERI)
- I am an adviser for the SIPH
- I am an oncologist and Head of Department
Oncology and Genomics
Tests are done on all Levels - daily

- Body
- Organ
- Tissue
- Cell

Which gene-test?  Which diagnosis?
Oncology and Genomics
Tests are done on all Levels - daily

∙ Protein
∙ Chromosomes
∙ RNA
∙ DNA  FISH

Mutations and more...
Hereditary Breast und Ovarian Cancer-Syndrom HBOC

The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services


• +100% BRCA mutation analyses
• Increase in prophylactic mastectomies and plastic surgery

Angelina Jolie Effect > prolonged global increase in genetic counseling
The Wave
Genetic Counseling
Breast Center KSSG

Anzahl Erstkonsultationen Genetik

- Erstberatungen Genetik
- KSSG
- Grabs
- extern

2014
2015
2016

1 MedOnc
0.1 Med Geneticist

5 MedOnc
2 Surgeon
0.1 Med Geneticist
Molecular Genetic Analysis

- NGS-Method (Next Generation Sequencing)
  faster, cheaper, more genes (Panel)

  ➢ **Germline testing** genetic analysis on healthy tissue
    *Speziallabs for Medical Genetics*
    GUMG, genetic counseling mandatory, request for cost coverage

  ➢ **Somatic testing** genetic testing on tumor tissue
    *Institute for Pathology, different legal regulations*
    GUMG revision, excess information

**Interpretation of test results**
> Knowledge and experience of the lab is absolutely key

**Transport and application of test results**
> Knowledge and experience of the interdisciplinary team is key
How is allowed to order germline genetic testing?

Bundesgesetz über genetische Untersuchungen beim Menschen (GUMG)

Art. 13 Veranlassen genetischer Untersuchungen
1 Genetische Untersuchungen dürfen nur von Ärztinnen und Ärzten veranlasst werden, die zur selbständigen Berufsprüfung oder als Genehmigung ihrer Aufsicht befugt sind.
2 Präsymptomatische Untersuchungen sowie Untersuchungen von Eltern für Kinder, die veranlasst werden, müssen von Ärztinnen und Ärzten vorbereitet werden, die entsprechende Weiterbildung in der Berufsprüfung oder die im Rahmen ihrer Weiterbildung im Sinne der Berufsprüfung durchgeführt haben.
3 Ärztinnen und Ärzte, die eine genetische Untersuchung nach Absatz 2 veranlasst, sorgen für die Vor- und Nachbesprechung und die Beratung der Patienten.

KLV Art. 12d f

No molecular genetic germline analysis without genetic counseling!

Reimbursement for members only!

Only in certified + supervised labs!

CPTC-Netzwerk
Cancer Predisposition Testing and Counseling
Regulations and Access

• are a problem because
  - lacking behind the technology
  - clinical + cost-benefit evidence cannot be or is not generated fast enough

• only 4 cancer syndromes have a reimbursement regulation through KLV
  - HBOC, HNPCC, polyposis coli, retinoblastoma
  - Ordonances are exclusive
Genetic HBOC Testing and

- > increase in surveillance
- > massive increase in prophylactic surgery both in patients and heathy women
- > massive increase in plastic surgery: DIEP
Genetic HBOC Testing and

- 2 operation teams, 4 surgeons 8-9 h
- and specialised nursing for surveillance on specialised ward
- and....
Genetic HBOC Testing and

- and 6-12 months
- and some minor surgeries later
Genetic Testing on Tumor Tissue/Cells

· is routine on all biological levels
· varies widely across tumor types and drugs available

· Examples of medical management today
  · Testicular Cancer
  · Lung Cancer
  · Breast Cancer
Testicular Cancer

- No testing is done
- No molecular target is available
- No targeted drug is available
- Patients receive surgery and chemotherapy
- Almost all patients are cured with surgery and chemotherapy, even in advanced stage
Genetic Testing on Tumor Tissue/Cells

- is routine on all biological levels
- varies widely across tumor types and drugs available

- Example: Lung Cancer today
Lung Cancer

- Sub-type of lung cancer
- NSCLC
- Adeno, squamous, other, mixed
- Mutation panel

Treatment with Alk-Inhibitors:

- Crizotinib
- Ceritinib

More than 1 mutation?
How do they work together?

Do you want to be an oncologist?
Treatment with ALK Inhibitors

sustained chemo response < 10%

ALK-Inhibitor response rate > 60%
time to progression 13.4, months

Relative rapid resistance

Costs:
CHF 69’000 /y
CHF 74’000 /y
Genetic Testing on Tumor Tissue/Cells

- is routine on all biological levels
- varies widely across tumor types and drugs available

- Example Breast Cancer
Breast Cancer: Prognostic and Predictive Markers

- Patient A.V., born 17.01.81
- Diagnosis: Invasive breast cancer left NST
  pT1c, pN2a (8/10), G2, BRE Score 6 (3,2,1)
  L1 focal, V0, ED 12/12
  ER 90% IRS 12/12, PgR 100%, IRS 12/12
  HER2 Dako-ICH: Score 2+,
  FISH Pathvision: ratio 1.19, gene copy number 2.4
  Ki-67 17%
Breast Cancer: 3 Primary Considerations

- Magnitude of risk of recurrence after surgery? Does the patient need further therapy to prevent spread of the tumor? **Prognostic info**

- If yes, how much can she benefit (relative and absolute) from which treatment? **Predictive info**

- and..how robust are the answers generated by the tests?
Breast Cancer: Prognostic and Predictive Markers

IHC

Zytologische Diagnose

RSC/ns

ZUSATZBERICHT:

FNP Lymphknoten supraklavikulär rechts: Zellen eines nicht-kleinzelligen Karzinoms, vereinbar mit Mammakarzinom.

Expression von Östrogenrezeptor in 90% der Tumorzelkerne.
Expression von Progesteronrezeptor in 100% der Tumorzelkerne.

Mikroskopischer Befund

RSC

8311:

Östrogenrezeptor (Clone ER-6F11 Novocastra):
Färbereaktion: stark (Grad 3)
Anzahl positive Zellen: > 80% (Grad 4)

Progesteronrezeptor (Clone 16 Novocastra):
Färbereaktion: stark (Grad 3)
Anzahl positive Zellen: > 80% (Grad 4)

Ergebnis der semiquantitativen immunhistochemischen Hormonrezeptorenbestimmung (Immunreaktiver Score (IRS) nach Remmele W.; Stegner H.: Pathologe 8 (1987); 138-140):
Östrogen-ImmunReaktiver Score: 12 = stark positiv
Progesteron-ImmunReaktiver Score: 12 = stark positiv
Breast Cancer: Prognostic and Predictive Markers

RNA 21-gene-signature

FISH

Diagnose 2235:

HER2 Genstatus (entsprechend ASCO/CAP Konsensus J Clin Oncol 2013; 31:3997-4013):
ISH NEGATIV bei HER2/CEP17 Ratio von 1.1 und HER2 Genzahl von 2.1
(ISH Negativ: Ratio < 2.0 und HER2 Genzahl < 4.0)

Spezialuntersuchung
Die HER2 FISH wurde mit dem PathVysion® HER-2 DNA Probe Kit (Abbott Molecular) durchgeführt.

Es wurden 60 Karzinomzellen ausgezählt:
HER2-Genzahl (Durchschnitt): 2.1
HER2-Genzahl (Spanne): 1-4 Kopien pro Tumorzellkern
CEP17-Zahl (Durchschnitt): 2.0
CEP17-Zahl (Spanne): 1-3 Kopien pro Tumorzellkern
Locus Cluster: 0% der Tumorzellkerne
Centromer Cluster: 0% der Tumorzellkerne
HER2 Genzahl (Summe) / CEP17-Zahl (Summe): 128/121
Ratio (HER2-Genzahl (Summe) / CEP17-Zahl (Summe)): 1.1
HER2 genetische Heterogenität: 0%
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Breast Cancer: Prognostic and Predictive Markers

red: prognostic only

green – blue – orange: prognostic and predictive

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From Tumor-Biology to Treatment of the Patient Breast Cancer

Step 1

- Standard information from pathology
- Assess recurrence risk
- Assess predictive chance and magnitude of risk reduction by
  - Anti-hormonal treatment
  - Chemotherapy
  - Anti-HER2 therapy
  - Other available drugs
From Tumor-Biology to Treatment of the Patient
Breast Cancer
Steps 2 - 6

- Assess biology and pharmacologic options
- Assess host (age, organs function, co-morbidities, medication, socio-cultural background)
- Make recommendation(s) and give alternatives
- Ask for patient preference
- Discuss
- Come to a reasonable conclusion
- Implement treatment
When you have no Standard Therapy (any more)

- Tumor gene profiling
  - Fishing for «drug-able targets»
    - mutations, overexpression, gene-amplification or deletions, silenceing ...
    - Gene-interactions? Driver and passengers? Is only a screenshot!
  - In most cases not useful
    - Genetic aberration not actionable, technical limitations, no drugs developed, not examined, not available, not accessable ...
    - Usually < 10% accessible and <5% benefit
Summary:
Technology is the Driver
Access and Complexity are the Obstacles

· Genetic germline aberrations
  · The wave and it’s consequences for individuals and society
  · Still, most cases of familiarity are unexplained

· If it comes to treatment, biology is the most important factor
  · Wide variation on need, use and opportunities
The future: Opportunities and Limitations

**Opportunities**
- Starts now
- Better personalised prognosis
- Better personalised prediction
- Liquid biopsy
- Repair (CRISPR) defects
- Repair resistance
- Potentially cheap
- Potentially easy to apply

**Limitations**
- Faster than we can deal
- Better personalised prognosis
- Better personalised prediction
- Overdiagnosis
- Overfeeding > needs teams
- Drugs lag behind (Dg>>Rx)
- Access
- Drugs are usually quite toxic and not easy to handle
Genetics and Genomics in Precision Medicine 2018

Optimist | Pessimist | Ingenieur | Realist
---|---|---|---
half full | half empty | Glass has double size it should have | Glass is full half water half air
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