Spectrum of challenges of HCP in terms of adapting to the complex and rapidly changing cancer treatment paradigms and with respect to doctor - patient communication

On Equality in Beating Cancer

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18.03.2022.

Disclosures

Advisory boards and speaker fees: Amgen, Astra Zeneca, Eli Lilly, MSD, Novartis, Roche

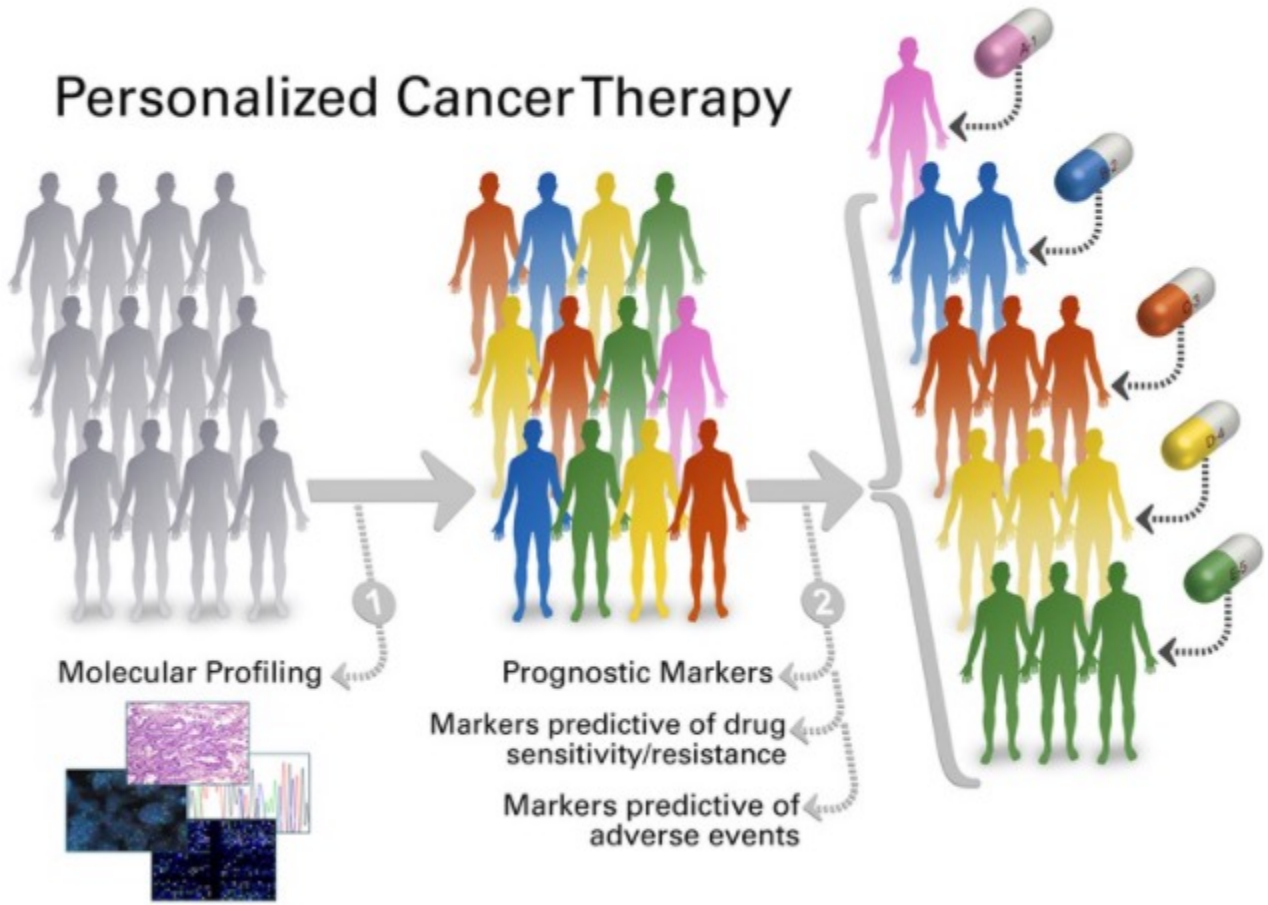
- Every person is unique
- So is every cancer

NIH National Cancer Institute

Personalised Medicine

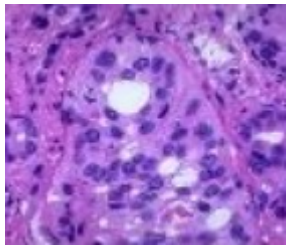
A form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease.

In cancer, personalized medicine uses specific information about a person's tumor to help make a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis.


Personalized Cancer Therapy
1
Molecular Profiling
2
Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events

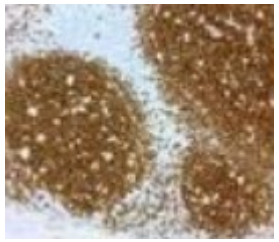
Histological (Tissue) Testing

Hematoxilin&Eosin staining



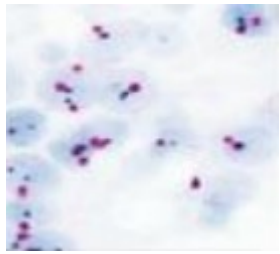
One of the principal tissue stains used in histology.
Hematoxylin stains cell nuclei blue, eosin stains the extracellular matrix and cytoplasm pink

Immunohistochemistry (IHC)



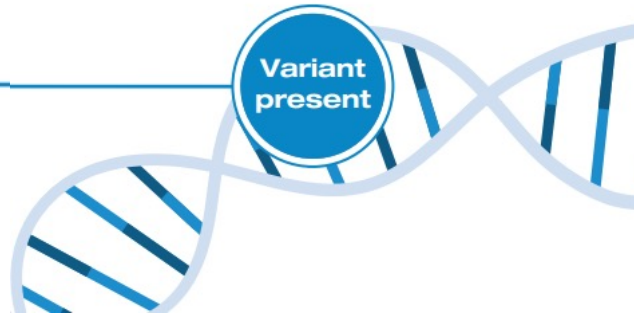
Selectively identifies antigens (proteins) in cells, to detect the presence of a specific protein marker that can assist with accurate tumor classification and diagnosis

In Situ Hibridization (ISH)



Uses a labeled complementary DNA, RNA probes to localize a specific DNA or RNA sequence in tissue
FISH, CISH

Molecular Testing



qPCR

qPCR allows for the analysis of particular variants at specific locations.

Benefits

- High sensitivity
- Quick and simple workflow
- Capital equipment already found in most labs

Limitations

- Only examines a small set of variants
- Virtually no discovery power[1-4]
- Low variant resolution[1-4]
- Low scalability[5]

Targeted NGS

Targeted NGS simultaneously screens several hundred to thousands of genes.

Benefits

- Expanded discovery power through comprehensive genomic coverage
- Higher analytical sensitivity[6,7]
- Greater resolution of genomic variants[1-4]
- More data from smaller DNA amounts[5]
- Higher throughput with sample multiplexing[5]

Limitations

- May be less cost effective when interrogating a low number of samples
- Requires a dedicated data-handling workflow

Comprehensive Genomic Profiling CGP

Analyses known cancer-relevant genes (tumor genome)

Prophylaxis

- Earlier diagnosis- personalized screening for high-risk populations

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NCCN Guidelines Version 2.2022
***BRCA*-Pathogenic/Likely Pathogenic Variant - Positive Management**

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Discussion

***BRCA* PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT**

GENERAL

- **Education regarding signs and symptoms of cancer(s), especially those associated with *BRCA* gene pathogenic/likely pathogenic variants.**

BREAST CANCER

- **Female**
  - **Breast awareness[a] starting at age 18 years.**
  - **Clinical breast exam, every 6–12 months,[b] starting at age 25 years.**
  - **Breast screening[c,d]**
    - **Age 25–29 years, annual breast MRI[e] screening with contrast[f] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.**
    - **Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI[e] screening with contrast.**
    - **Age >75 years, management should be considered on an individual basis.**
    - **For individuals with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram with consideration of tomosynthesis and breast MRI should continue as described above.**
  - **Discuss option of risk-reducing mastectomy**
    - **Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.**
  - **Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.**
- **Consider risk reduction agents as options for breast cancer, including discussion of risks and benefits (See Discussion for details). (See NCCN Guidelines for Breast Cancer Risk Reduction).**
- **Male**
  - **Breast self-exam training and education starting at age 35 years.**
  - **Clinical breast exam, every 12 months, starting at age 35 years.**
  - **Consider annual mammogram screening in men with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family (whichever comes first).[g]**

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

[a] Females should be familiar with their breasts and promptly report changes to their health care provider. Periodic, consistent breast self exam (BSE) may facilitate breast self awareness. Premenopausal individuals may find BSE most informative when performed at the end of menses.

[b] Randomized trials comparing clinical breast exam versus no screening have not been performed. Rationale for recommending clinical breast exam every 6–12 mo is the concern for interval breast cancers.

[c] The appropriateness of imaging modalities and scheduling is still under study. Lowry KP, Lee JM, Kong CY, et al. Cancer 2012;118:2021-2030.

[d] Lehman CD, et al. J Natl Cancer Inst 2016;108.

[e] The criteria for high-quality breast MRI include a dedicated breast coil, the ability to perform biopsy under MRI guidance, radiologists experienced in breast MRI, and regional availability. Breast MRI is preferably performed on days 7–15 of a menstrual cycle for premenopausal patients. FDA Drug Safety Communication: FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue.

[f] Breast MRI is preferred due to the theoretical risk of radiation exposure in pathogenic/likely pathogenic variant carriers.

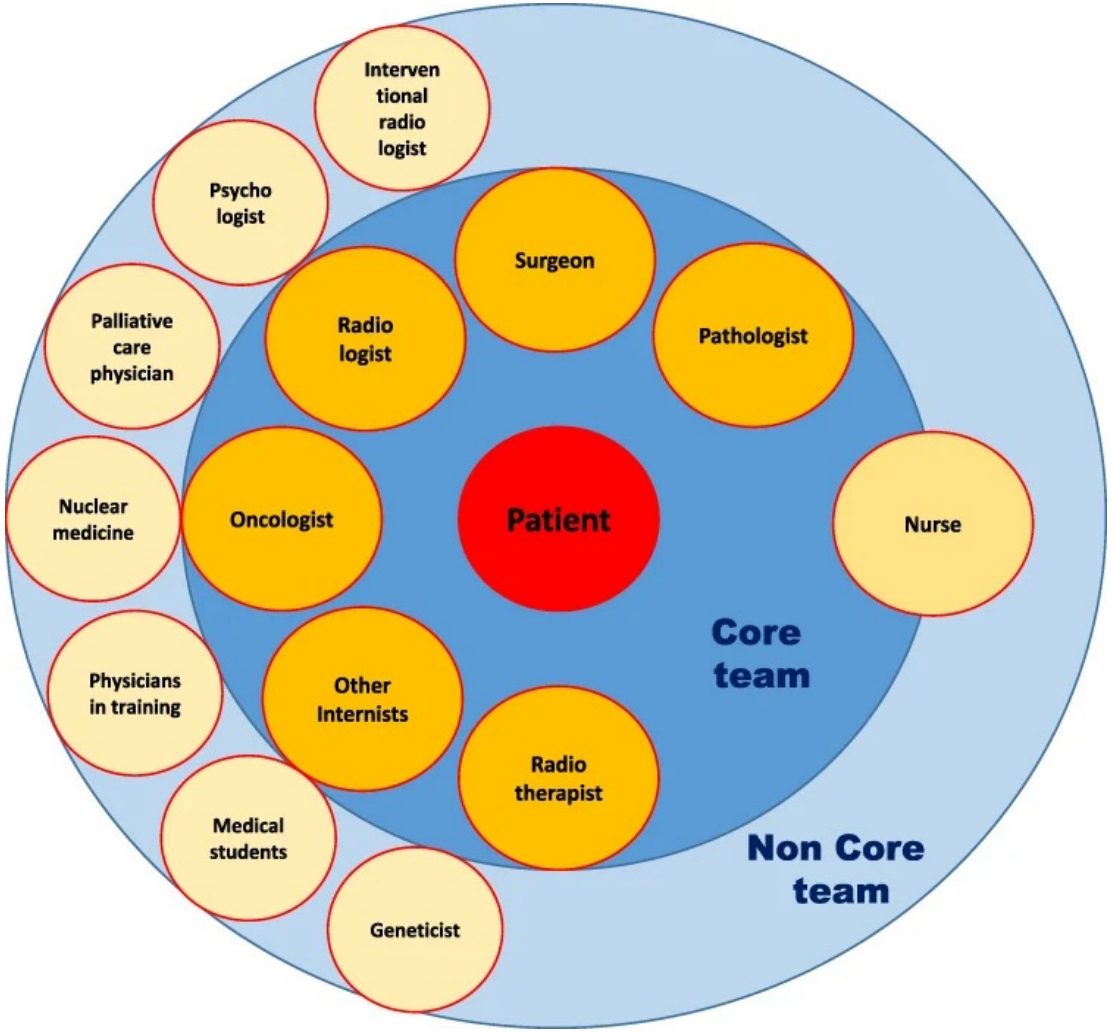
[g] There are only limited data to support screening for male breast cancer. Gao Y, et al Radiology 2019;293:282-291.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

- Prophylactic surgery

Multidisciplinary Approach

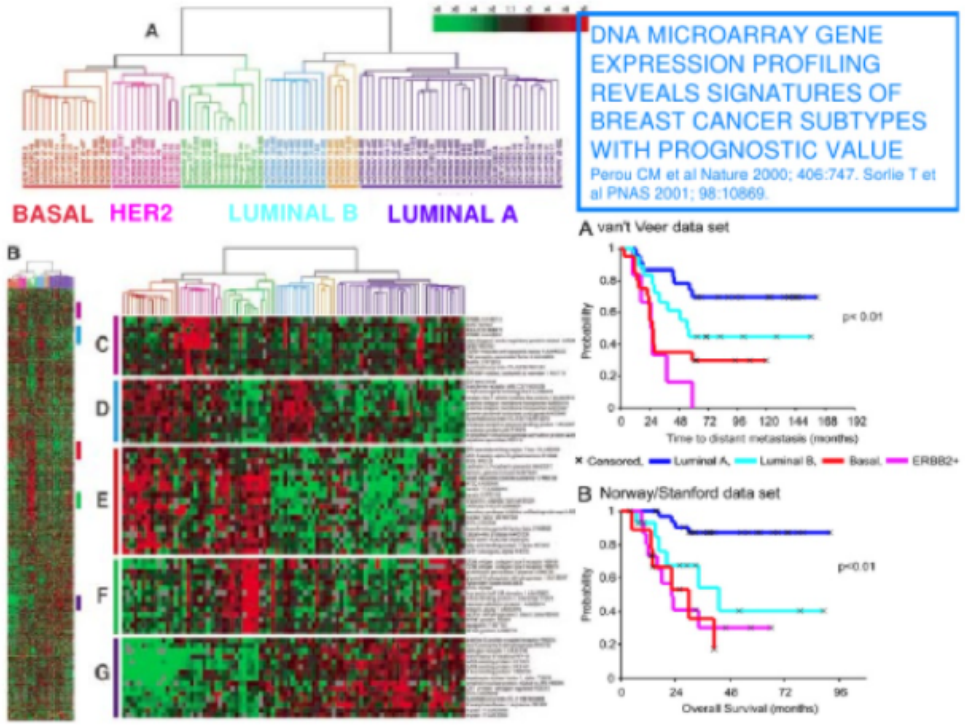


Cancer Treatment

The right medicine for the right patient at the right time

Targeted therapy is a cancer treatment that uses drugs to target specific genes and proteins that are involved in the growth and survival of cancer cells *(cancer.net)*

Breast Cancer Molecular Subtypes

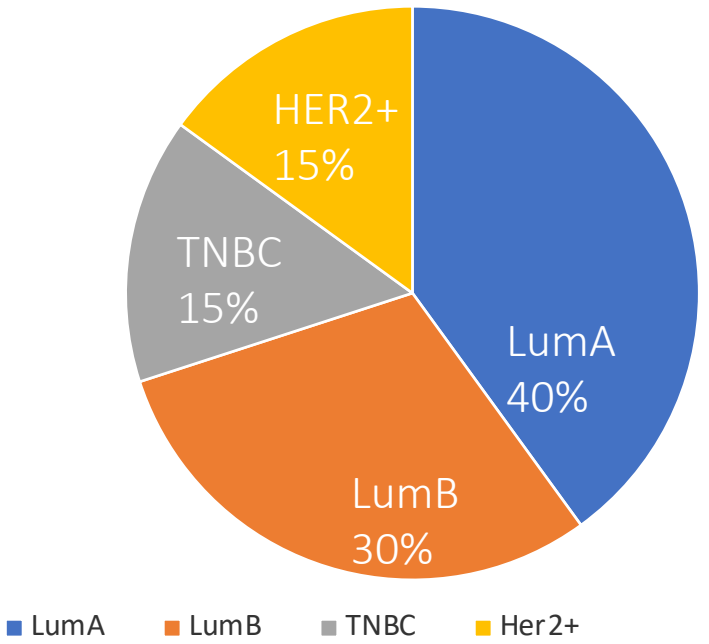


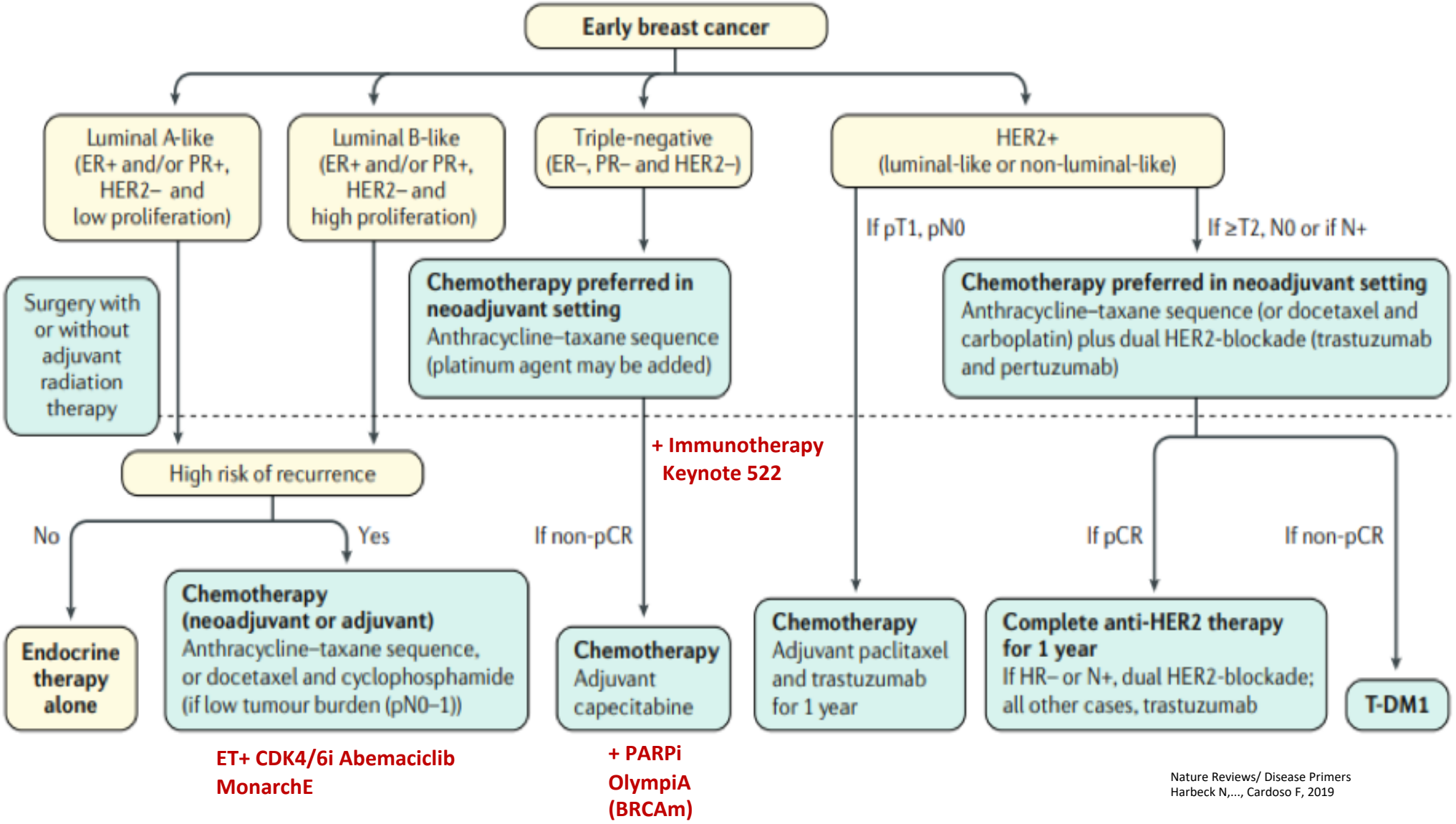
DNA MICROARRAY GENE EXPRESSION PROFILING REVEALS SIGNATURES OF BREAST CANCER SUBTYPES WITH PROGNOSTIC VALUE

Perou CM et al Nature 2000; 406:747. Sorlie T et al PNAS 2001; 98:10869.

Molecular BC Subtype Correlates with IHC

- Luminal A- ER/PR+, HER2-, low ki-67, G1
- Luminal B- ER/PR+, HER2-, high ki-67, G2/3
- Triple negative- ER/PR-, HER2-
- HER2 positive- ER/PR-, HER2+



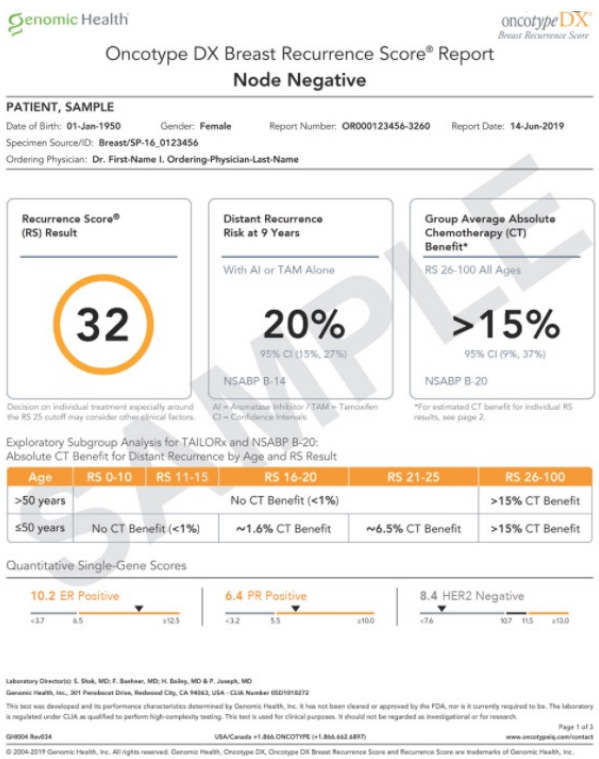


Nature Reviews/ Disease Primers
Harbeck N,..., Cardoso F, 2019

Adapted from Harbeck N,..., Cardoso F, 2019

Breast Cancer Risk of Recurrence
Oncotype DX

TAILORX (T≤ 5cm, N0), RxPONDER (T≤ 5cm, 1-3 l/m)



Genomic Health

oncotypeDX Breast Recurrence Score

Oncotype DX Breast Recurrence Score® Report

Node Negative

PATIENT, SAMPLE

Date of Birth: **01-Jan-1950** Gender: **Female** Report Number: **OR000123456-3260** Report Date: **14-Jun-2019**

Specimen Source/ID: **Breast/SP-16_0123456**

Ordering Physician: **Dr. First-Name I. Ordering-Physician-Last-Name**

Recurrence Score® (RS) Result

32

Decision on individual treatment especially around the RS 25 cutoff may consider other clinical factors.

Distant Recurrence Risk at 9 Years

With AI or TAM Alone

20%

95% CI (15%, 27%)

NSABP B-14

AI = Aromatase Inhibitor / TAM = Tamoxifen
CI = Confidence Intervals

Group Average Absolute Chemotherapy (CT) Benefit*

RS 26-100 All Ages

>15%

95% CI (9%, 37%)

NSABP B-20

*For estimated CT benefit for individual RS results, see page 2.

Exploratory Subgroup Analysis for TAILORx and NSABP B-20:
Absolute CT Benefit for Distant Recurrence by Age and RS Result

Age	RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
>50 years			No CT Benefit (<1%)		>15% CT Benefit
≤50 years	No CT Benefit (<1%)		~1.6% CT Benefit	~6.5% CT Benefit	>15% CT Benefit

Quantitative Single-Gene Scores

10.2 ER Positive (<3.7, 6.5, ≥12.5)

6.4 PR Positive (<3.2, 5.5, ≥10.0)

8.4 HER2 Negative (<7.6, 10.7, 11.5, ≥13.0)

Laboratory Director(s): S. Shak, MD; F. Baehner, MD; H. Bailey, MD & P. Joseph, MD

Genomic Health, Inc., 301 Penobscot Drive, Redwood City, CA 94063, USA - CLIA Number 05D1018272

This test was developed and its performance characteristics determined by Genomic Health, Inc. It has not been cleared or approved by the FDA, nor is it currently required to be. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

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GH004 Rev034 USA/Canada +1.866.ONCOTYPE (+1.866.662.6897) www.oncotypeiq.com/contact

Oncotype DX Breast Recurrence Score® Report

Node Negative

oncotypeDX Breast Recurrence Score

Date of Birth: **01-Jan-1950** Gender: **Female** Report Number: **597-01** Report Date: **05-Aug-2015**

Specimen Source/ID: **Breast/C83L0ZF1N**

Ordering Physician: **Dr. Harry D Smith**

Recurrence Score® (RS) Result

13

Decision on individual treatment especially around the RS 25 cutoff may consider other clinical factors.

Distant Recurrence Risk at 9 Years

With AI or TAM Alone

4%

95% CI (3%, 5%)

TAILORx

AI = Aromatase Inhibitor / TAM = Tamoxifen
CI = Confidence Intervals

Group Average Absolute Chemotherapy (CT) Benefit*

RS 11-25 All Ages

<1%

95% CI (-1%, 2%)

TAILORx

*For estimated CT benefit for individual RS results, see page 2.

Exploratory Subgroup Analysis for TAILORx and NSABP B-20:
Absolute CT Benefit for Distant Recurrence by Age and RS Result

Age	RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
>50 years			No CT Benefit (<1%)		>15% CT Benefit
≤50 years	No CT Benefit (<1%)		~1.6% CT Benefit	~6.5% CT Benefit	>15% CT Benefit

Quantitative Single-Gene Scores[1]

10.0 ER Positive (<3.7, 6.5, ≥12.5)

8.7 PR Positive (<3.2, 5.5, ≥10.0)

8.8 HER2 Negative (<7.6, 10.7, 11.5, ≥13.0)

1. ER Score based on quantitative ESR1 expression (estrogen receptor); PR Score based on quantitative PGR expression (progesterone receptor); HER2 Score based on quantitative ERBB2 expression.

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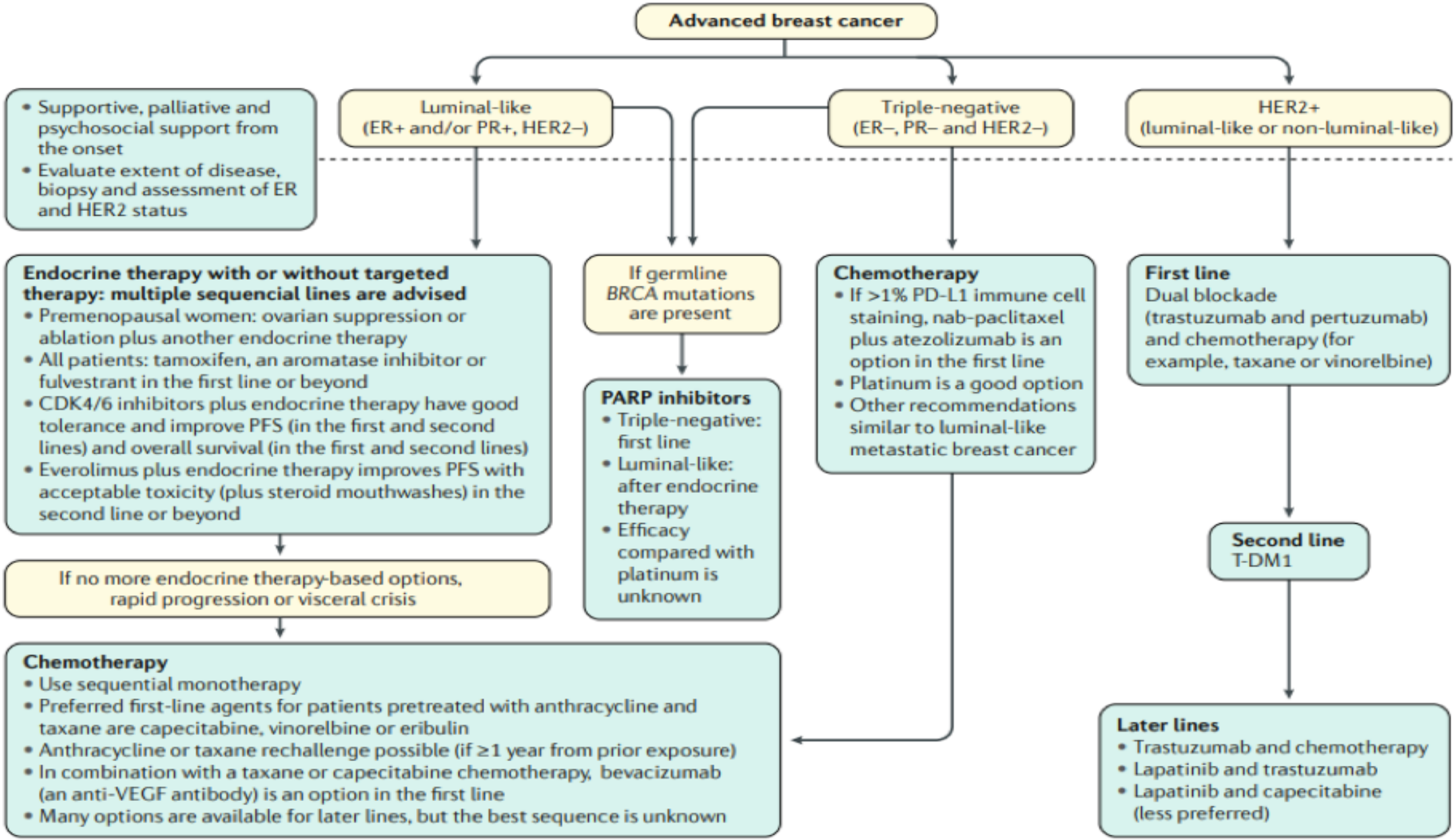
Sparano et al. N Engl J Med 2018; 379:111-121

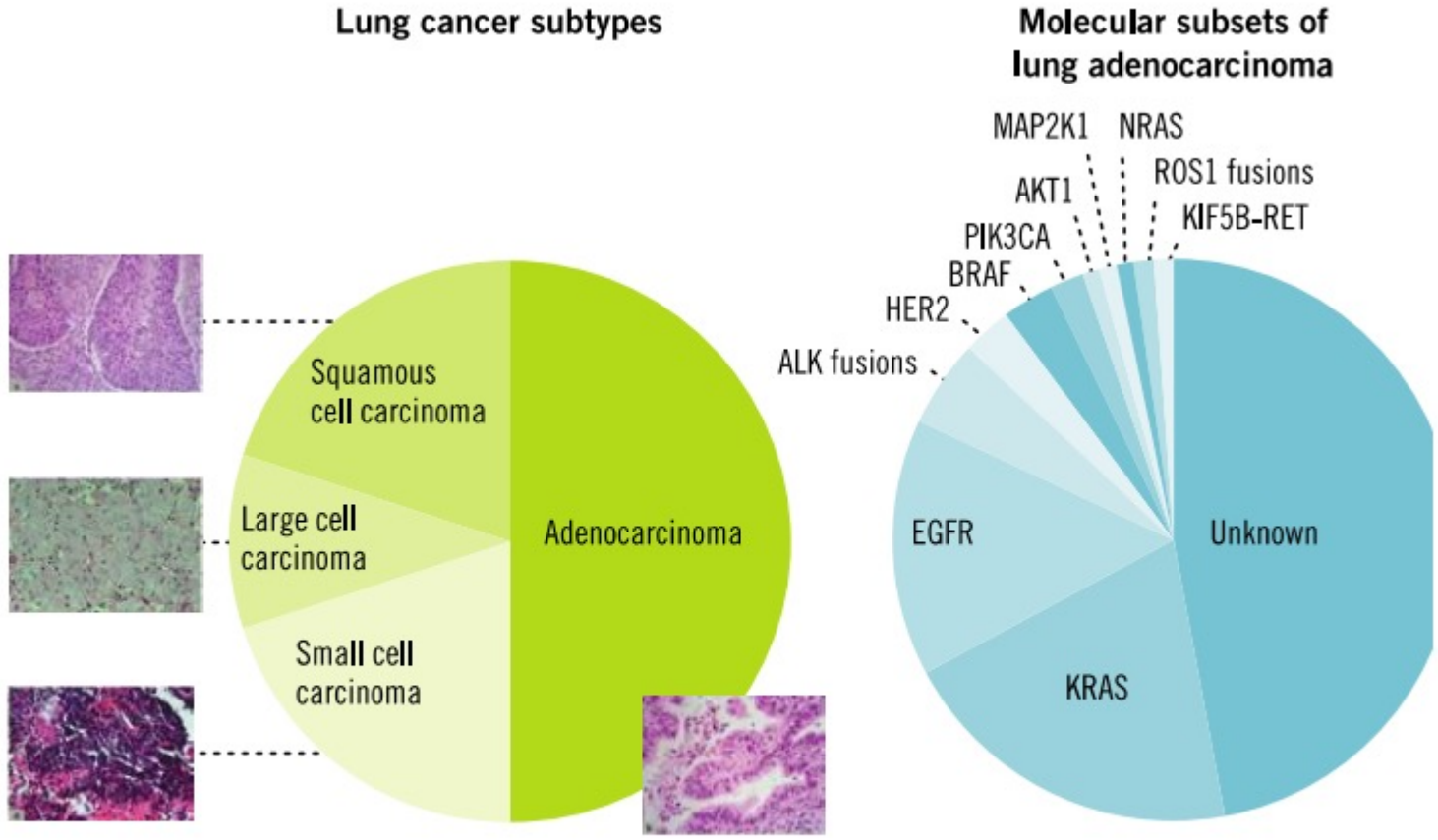
Kalinsky et al. N Engl J Med 2021; 385:2336-2347



Nature Reviews/ Disease Primers
Harbeck N,..., Cardoso F, 2019

Lung Cancer-Not One Disease

Histological and Molecular Subtypes of Lung Cancer



Adapted from Petersen I. Dtsch Arztebl Int 2011; 108(31-32):525-531 (left) and Pao W & Hutchinson KE. Nature Med 2012; 18(3): 349-351,

NSCLC Treatment

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Non-Small Cell Lung Cancer

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D

TESTING RESULTS[ll,mm]

EGFR exon 19 **deletion or** ***L858R*** **mutation positive**	NSCL-20
EGFR S768I, L861Q, **and/or** ***G719X*** **mutation positive**	NSCL-23
EGFR exon 20 **insertion mutation positive**	NSCL-24
KRAS G12C **mutation positive**	NSCL-25
ALK **rearrangement positive**	NSCL-26
ROS1 **rearrangement positive**	NSCL-29
BRAF **V600E mutation positive**	NSCL-31
NTRK1/2/3 **gene fusion positive**	NSCL-32
METex14 **skipping mutation positive**	NSCL-33
RET **rearrangement positive**	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

[ll] If there is insufficient tissue to allow testing for all of *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET,* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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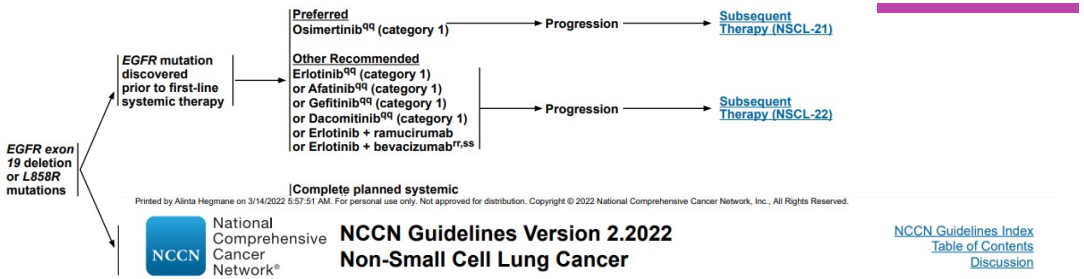
EGFR EXON 19 **DELETION OR** ***L858R*** **MUTATIONS[mm]**

FIRST-LINE THERAPY[pp]



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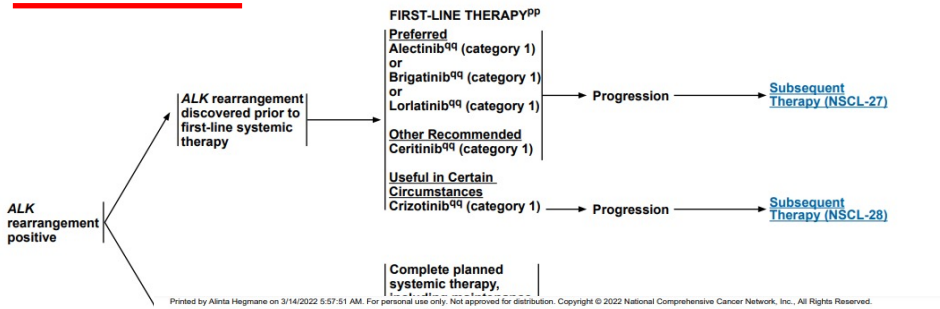
ALK **REARRANGEMENT POSITIVE[mm]**

FIRST-LINE THERAPY[pp]



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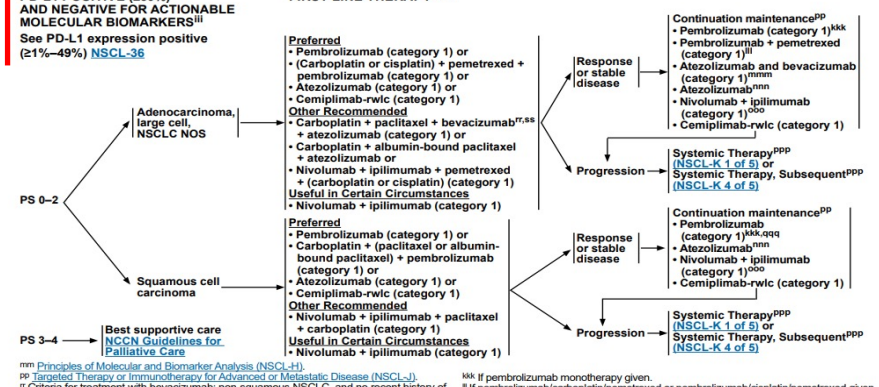
PD-L1 POSITIVE (≥50%)[mm] AND NEGATIVE FOR ACTIONABLE MOLECULAR BIOMARKERS[lll]
See PD-L1 expression positive (≥1%–49%) NSCL-36

FIRST-LINE THERAPY[pp,jjj]

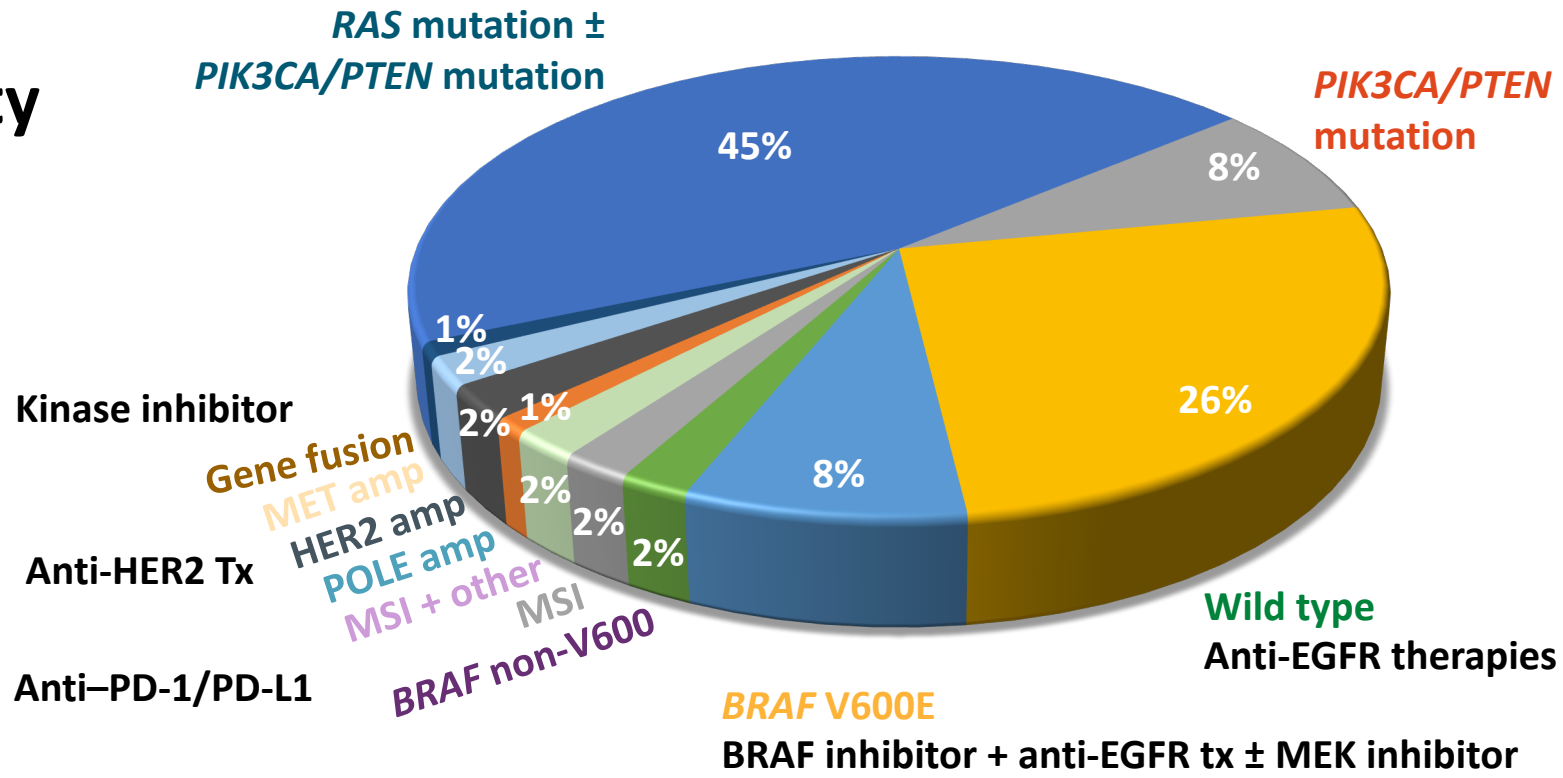


[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[kkk] If pembrolizumab monotherapy given.

Biomarker Testing in Colorectal Cancer (CRC)

- For all colon cancers:
  - **MMR**
  - **Microsatellite stability**
- Metastatic disease:
  - ***KRAS, NRAS, BRAF***
  - ***HER2* amplification**
  - **Panels: ± fusion, broad NGS**

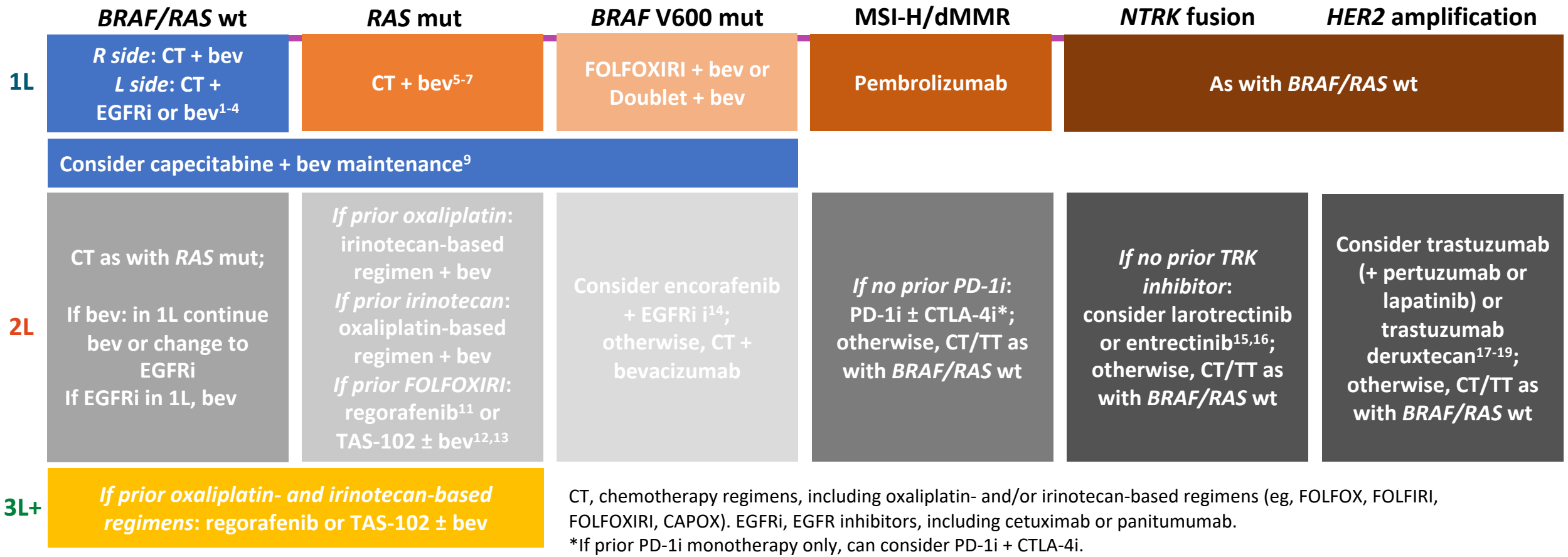
Molecular Classification of CRC and Associated Targeted Therapies



Dienstmann. Am Soc Clin Oncol Educ Book. 2018;38:231.

Slide credit: clinicaloptions.com

mCRC Treatment Algorithm



CT, chemotherapy regimens, including oxaliplatin- and/or irinotecan-based regimens (eg, FOLFOX, FOLFIRI, FOLFOXIRI, CAPOX). EGFRi, EGFR inhibitors, including cetuximab or panitumumab.
*If prior PD-1i monotherapy only, can consider PD-1i + CTLA-4i.

1. Tejpar. JAMA Oncol. 2017;3:194. 2. Venook. JAMA. 2017;317:2392. 3. Loupakis. NEJM. 2014;371:1609. 4. Cremolini. Lancet Oncology. 2020;21:497.
5. Parikh. Clin Cancer Res. 2019;25:2988. 6. Douillard. NEJM. 2013;369:1023. 7. Van Cutsem. JCO. 2011;29:2011. 8. Overman. Lancet Oncol. 2017;18:1182.
9. Overman. JCO. 2018;36:773. 10. Van Cutsem. NEJM. 2020;383:2207. 11. Grothey. Lancet. 2013;381:303. 12. Mayer. NEJM. 2015;372:1909. 13. Pfeiffer. Lancet Oncology. 2020;21:412. 14. Tabernero. JCO. 2021;39:273. 15. Hong. Lancet Oncol. 2020;21:531. 16. Doebele. Lancet Oncol. 2020;21:271.
17. Sartore-Bianchi. Lancet Oncol. 2016;17:738. 18. Meric-Bernstam. Lancet Oncol. 2019;20:518. 19. Siena. Lancet Oncol. 2021;22:779.

Slide credit: clinicaloptions.com

Summary

- From “one size fits all” towards personalized treatment in oncology
- Multidisciplinary approach
- Advances in pathology and molecular biology testing to choose the right treatment for the right patient
  - Actionable mutations might not be identified
  - Mutations identified might not driver mutations
  - Identification of “target” (driver mutations) does not help if there is no treatment available
- Considerable delays to get access to evidence based cancer treatments in Latvia

On Equality in Beating Cancer

Thank you!