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Effects of Co-Morbidities and Concomitant Medications on Immunotherapy Efficacy and Safety

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Disclosures

- Scientific Advisory Board: PhRMA Foundation, Empire Genomics, Ilera Healthcare
- Consultant: BMS, Incyte, Vertex, Idorsia, Chinese Academy of Science, United Cancer Center, Excelra
- No commercial or confidential information will be presented

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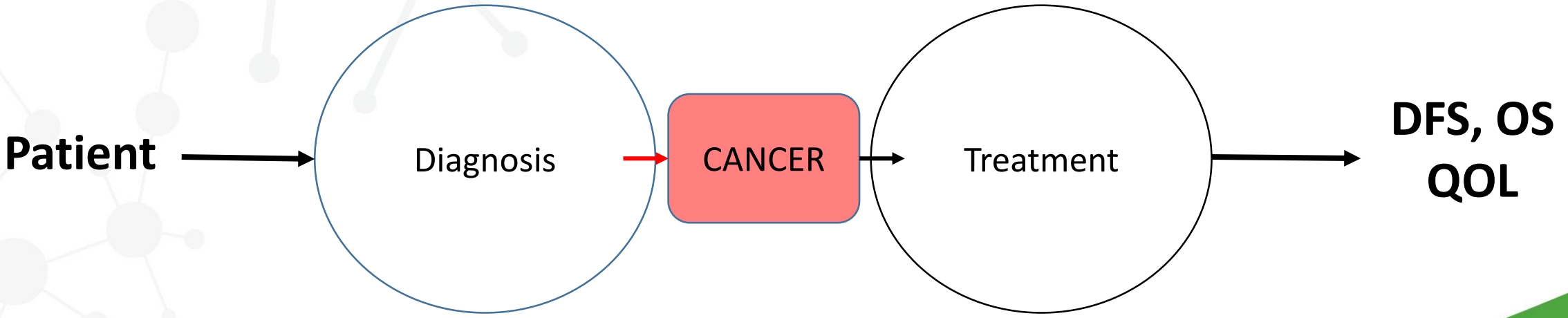
The Ideal Patient Journey



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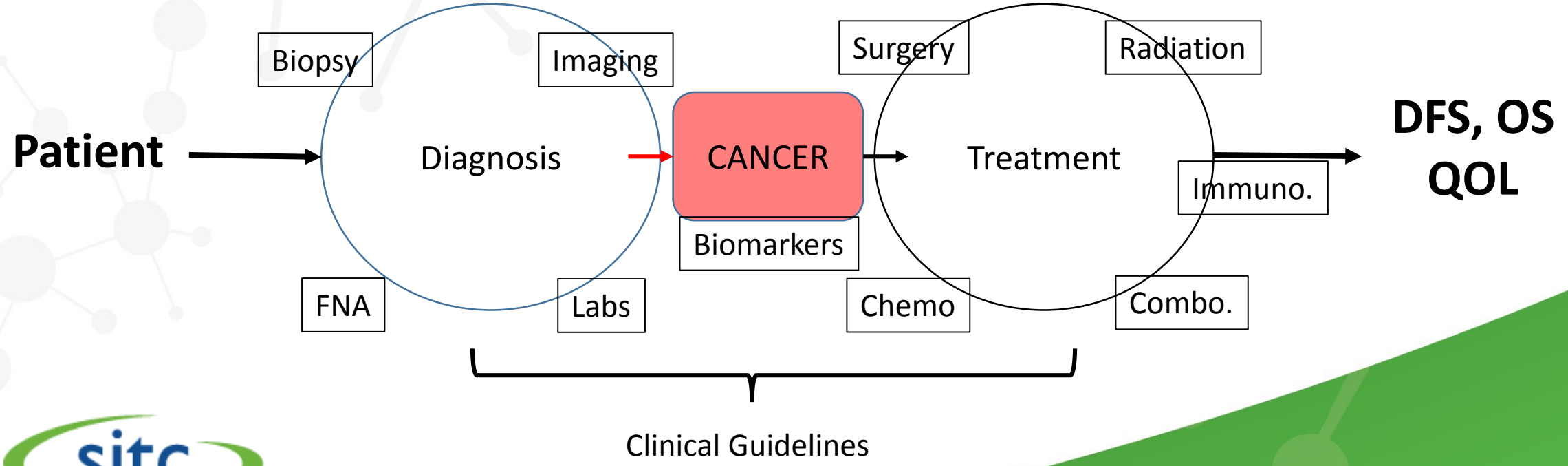
The Real Patient Journey



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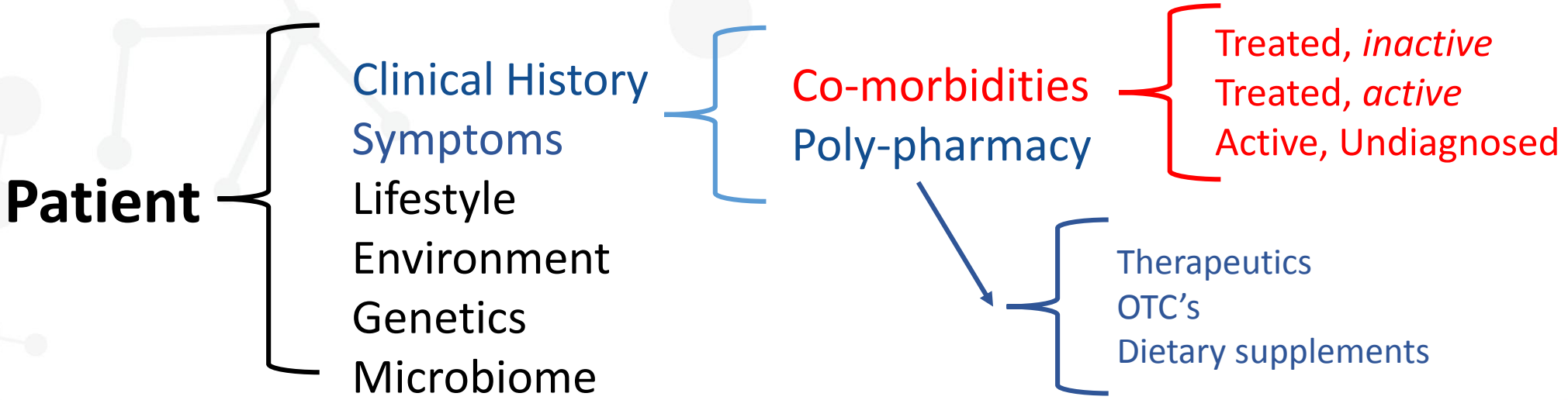
Real World Patients are Complex



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Co-morbidities

- “Comorbidity means more than one disease or condition is present in the same person at the same time” (CDC)
- Among Medicare beneficiaries **83% have at least one chronic condition** (more than 60% of patients diagnosed with cancer are 65 or older)
- A survey of members of a health maintenance organization ages 65 and over found the **average person had 8.7 chronic diseases**
- Among cancer patients: Lung (52.9%), colorectal (40.7%), breast (32.2), prostate (30.5%); NCI (2016)
- Common co-morbidities: arthritis, cardiac disease, depression, diabetes, dyslipidemia, hypothyroidism, hypertension, menopause, obesity, osteoporosis and osteopenia

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NCI Ranking of Comorbidities

- **Low comorbidity:** Usually won't require adjusting cancer treatments. May include conditions like ulcers or rheumatologic diseases.
- **Moderate comorbidity:** Conditions that may require the modification of cancer treatment. May include diabetes, vascular disease, paralysis, and AIDS.
- **Severe comorbidity:** Illnesses that always require modification of cancer treatment. May include diseases like COPD, liver dysfunction, dementia, and congestive heart failure.

Annual report to the nation on the status of cancer, 1975–2010
National Cancer Institute. (2016)

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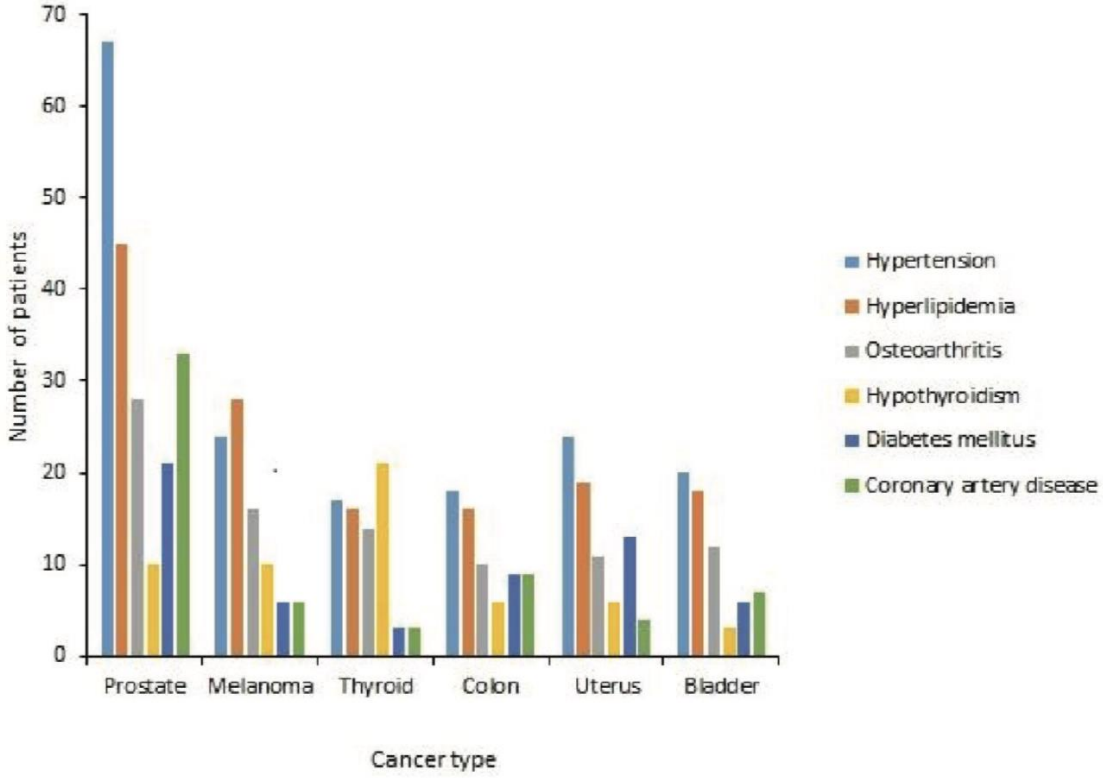

Figure 4. Frequencies of comorbid conditions in cancer survivors of top six types of cancers.

Comparison of Comorbid Conditions Between Cancer Survivors and Age-Matched Patients Without Cancer
Satyajeet Roy, Shirisha Vallepu, Cristian Barrios, Krystal Hunter J Clin Med Res 10(12) 911-919 (2018)

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Table A1. Prognostic Comorbidities by Cancer Type

Individual Comorbidities	Breast cancer	Colorectal cancer	Lung cancer
Cerebrovascular disease		X	
Chronic pulmonary disease	X	X	X
Congestive heart failure	X	X	X
Connective tissue disease			
Coronary artery disease	X		X
Dementia	X	X	X
Diabetes	X		X
Diabetes, end organ damage	X		
Gastrointestinal ulcer disease			
Hemiplegia/paraplegia	X		
Mild liver disease	X		
Moderate/severe liver disease		X	X
Moderate/severe renal disease	X	X	X
Morbid obesity*			
Other neurologic conditions*		X	
Peripheral vascular disease			X
Psychiatric disorder*			X
Substance abuse*		X	

*Individual comorbidities abstracted during the Special Study that are not a part of the Charlson-Deyo Comorbidity Index.

Comorbidity Assessment in the National Cancer Database for Patients With Surgically Resected Breast, Colorectal, or Lung Cancer (AFT-01, -02, -03).

Wong ML, McMurry TL, Schumacher JR, Hu CY, Stukenborg GJ, Francescatti AB, Greenberg CC, Chang GJ, McKellar DP, Walter LC, Kozower BD.

J Oncol Pract. 2018 Oct;14(10):e631-e643.

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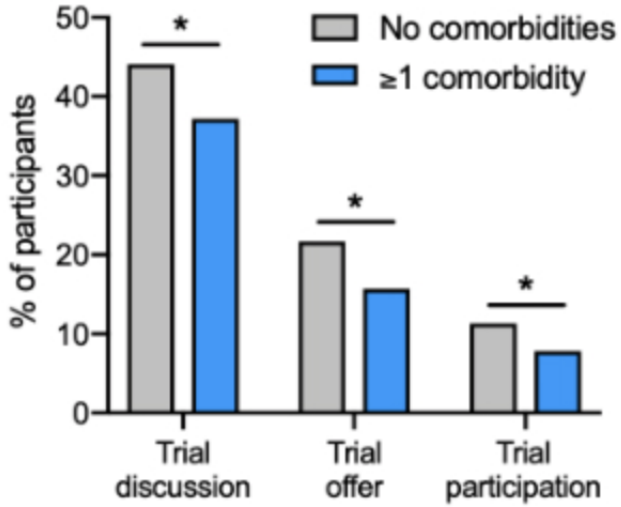
Limited Inclusion in Clinical Trials



Participant rates of clinical trial discussions, trial offers, and trial participation are significantly lower in patients with at least one comorbidity. *P<0.05.

Image by Maggie Burhans

Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation.
Unger JM, Hershman DL, Fleury ME, Vaidya R, JAMA Oncol. 2019 Mar 1;5(3):326-333

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Poly-Pharmacy

- “While the most commonly used definition of polypharmacy is being on five or more medicines, definitions are variable, which can cause confusion for researchers as well as clinicians in practice. Numerical definitions of polypharmacy do not account for specific comorbidities present and make it difficult to assess safety and appropriateness of therapy in the clinical setting.”

What is polypharmacy? A systematic review of definitions
Nashwa Masnoon, Sepehr Shakib Lisa Kalisch-Ellett, Gillian E. Caughey
BMC Geriatr. 2017; 17: 230.

- Need to consider drug-drug interactions, OTC, complementary and alternative medications, etc

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Table 2

Various numerical only definitions of polypharmacy and associated terms in existing literature

Term	Number of medications	Number of studies	References
Polypharmacy	≥ 2	1	[13]
	2 to 9	1	[14]
	≥ 3	1	[15]
	3 to 6	1	[16]
	≥ 4	6	[17–22]
	≥ 4 or ≥ 5	1	[23]
	≥ 5	51	[11, 24–73]
	≥ 6	10	[10, 74–82]
	≥ 7	2	[83, 84]
	5 to 9	3	[85–87]
	≥ 9	1	[88]
	≥ 10	1	[89]
	≥ 11	1	[90]
	number of drug classes	1	[91]
Minor Polypharmacy	2 to 4	6	[92–97]
	2 to 3	1	[98]
	0 to 4	1	[99]
Moderate polypharmacy	4 to 5	1	[98]
Major polypharmacy	≥ 5	6	[92–95, 97, 100]
	≥ 6	3	[96, 98, 101]
	5 to 9	1	[99]

What is polypharmacy? A systematic review of definitions
Nashwa Masnoon, Sepehr Shakib Lisa Kalisch-Ellett, Gillian E. Caughey
BMC Geriatr. 2017; 17: 230.

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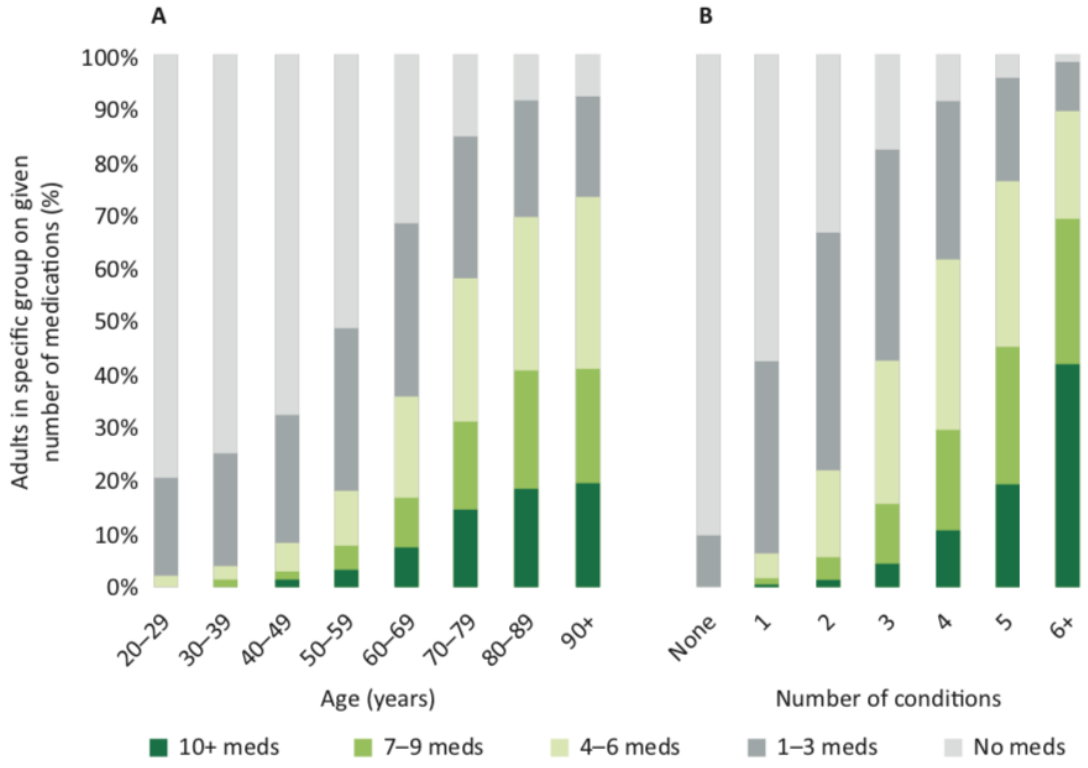

Fig 2. Percentage of Scottish adults on given number of medications by age (A) and number of conditions (B). Adapted with permission from Payne *et al.*[15]

The epidemiology of polypharmacy
Rupert A, PayneA
Clinical Medicine 2016 Vol 16, No 5: 465–9

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An update on the clinical consequences of polypharmacy in older adults: a narrative review, Jonas W. Wastesson, Lucas Morin, Edwin C.K. Tan & Kristina Johnell (2018) Expert Opinion on Drug Safety, 17:12, 1185-1196

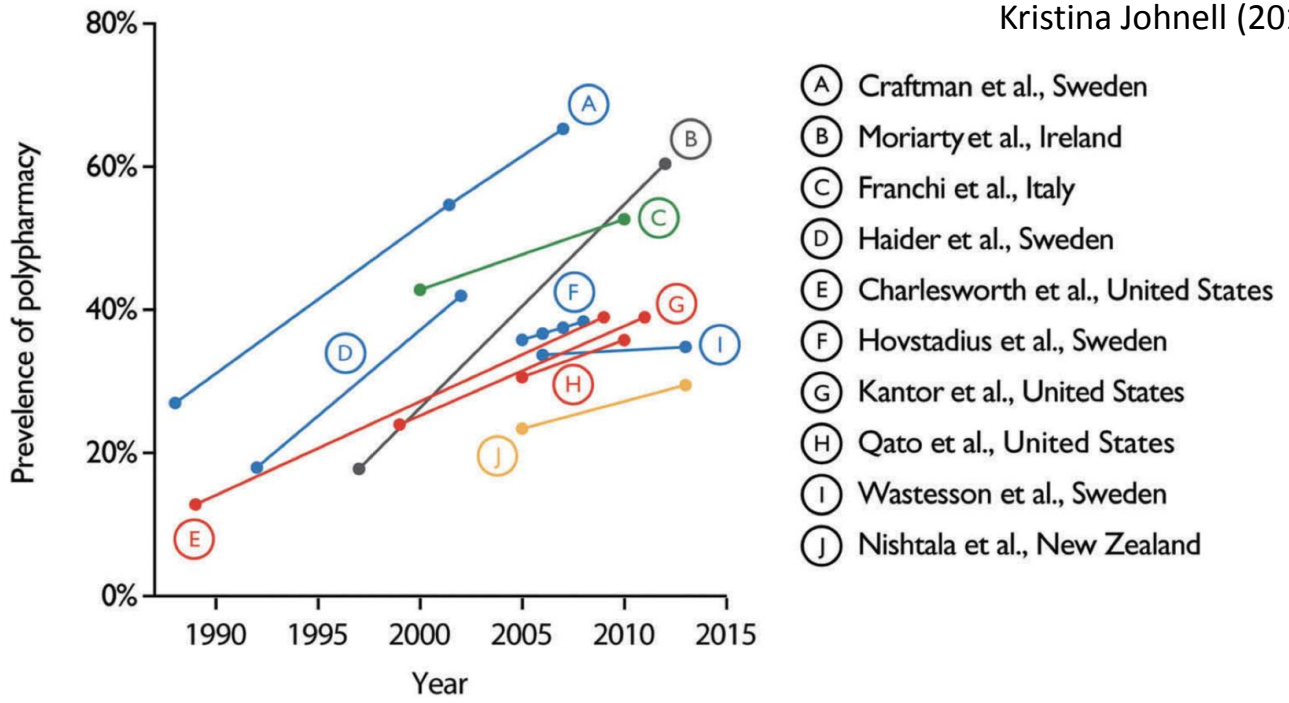

Figure 1. International trends in the prevalence of polypharmacy in older adults.

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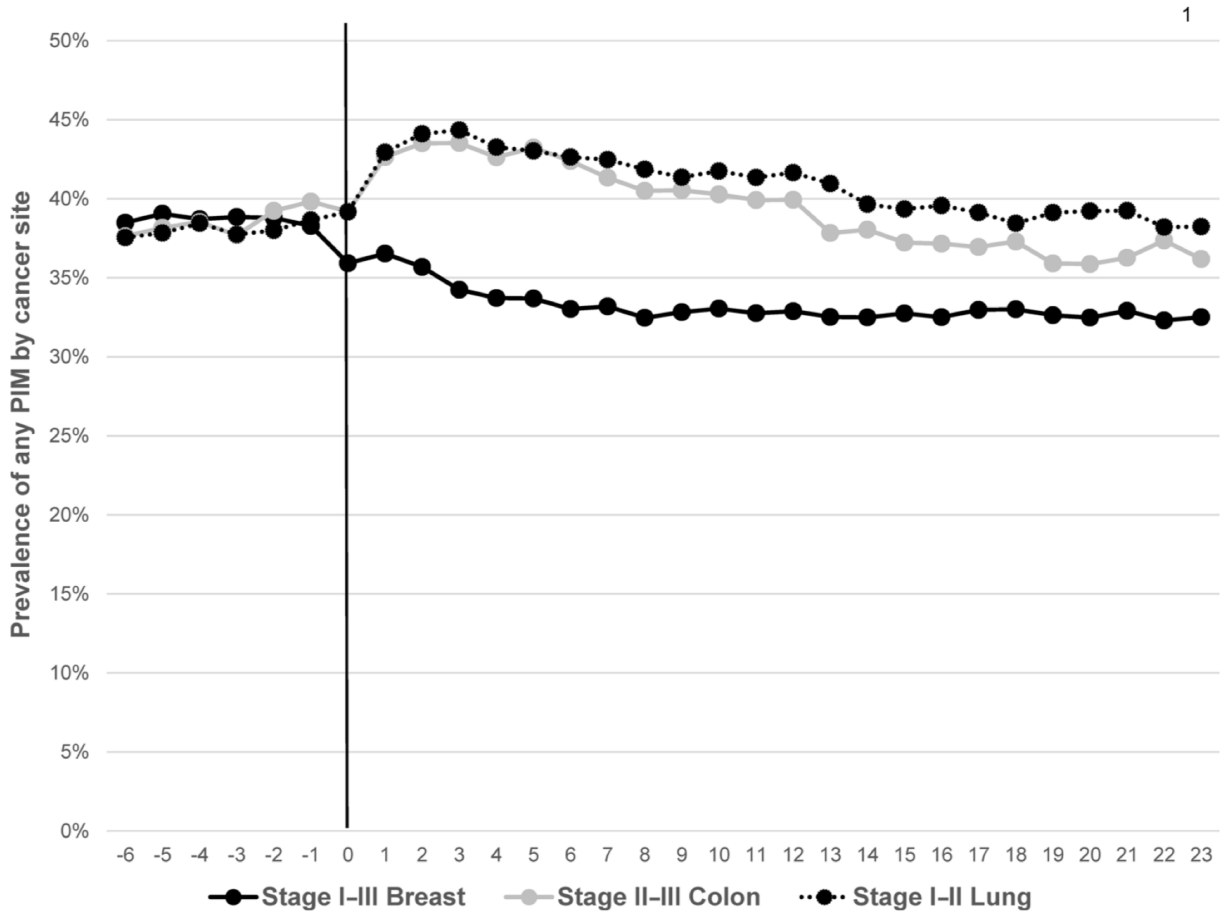

Figure 1.
Monthly prevalence of any PIM by cancer site from 6 months before through 23 months following the month of cancer diagnosis. The solid black line represents the stage I–III breast cancer cohort; the solid gray line represents the stage II–III colon cancer cohort; the dashed black line represents the stage I–II lung cancer cohort. The black vertical line denotes the month of cancer diagnosis.

Potential Medication-Related Problems in Older Breast, Colon, and Lung Cancer Patients in the United States
Jennifer L. Lund, Hanna K. Sanoff, Sharon Peacock-Hinton, Hyman Muss, Virginia Pate, and Til Stürmer
Cancer Epidemiol Biomarkers Prev. 2018 Jan; 27(1): 41–49.

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Co-morbidities
Poly-pharmacy

- Treated, *inactive*
- Treated, *active*
- Active, Undiagnosed

- autoimmune diseases
- ……..

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Autoimmune Diseases

- **80 autoimmune diseases**
  - https://www.niehs.nih.gov/health/topics/conditions/autoimmune/index.cfm
  - **1697 clinical trials (1351 recruiting currently)**
    - https://clinicaltrials.gov/search/open/condition=%22Autoimmune+Diseases%22
- **Affects more than 24 million people in the United States; additional eight million people have auto-antibodies**
  - **NIH Autoimmune Diseases Coordinating Committee: Progress in Autoimmune Diseases Research,** March 2005. (Last accessed July 19, 2019).
- **Diagnosis in auto-immune disease is commonly missed or mis-diagnosed**
  - **Diagnostic Testing and Interpretation of Tests for Autoimmunity** Christine Castro, D.O. and Mark Gourley, M.D. J Allergy Clin Immunol. 2010 Feb; 125(2 Suppl 2): S238–S247
- **The Auto-immune process can begin ~3.5 years prior to diagnosis**
  - **Autoimmunity and Cancer, the Paradox Comorbidities Challenging Therapy in the Context of Preexisting Autoimmunity**. Valencia JC, Egbukichi N, Erwin-Cohen RA, J Interferon Cytokine Res. 2019 Jan;39(1):72-84

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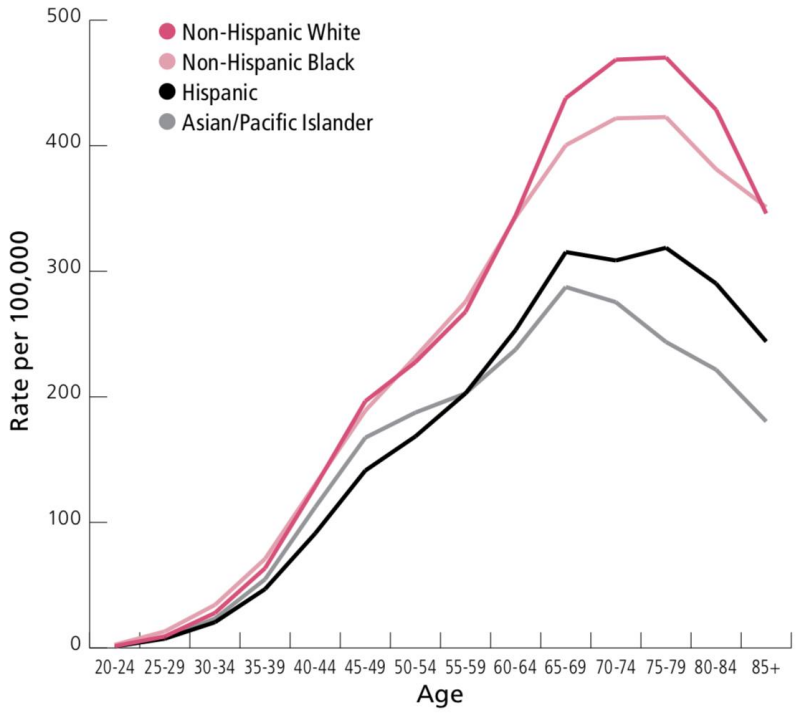
Breast Cancer

Figure 1. Age-specific Female Breast Cancer Incidence Rates by Race/Ethnicity, 2010-2014, US



Note: Rates are per 100,000 and age adjusted to the 2000 US standard population.

Sources: Incidence: North American Association of Central Cancer Registries (NAACCR), 2017. Mortality: National Center for Health Statistics, Centers for Disease Control and Prevention, 2017.

American Cancer Society, Inc., Surveillance Research, 2017

https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf

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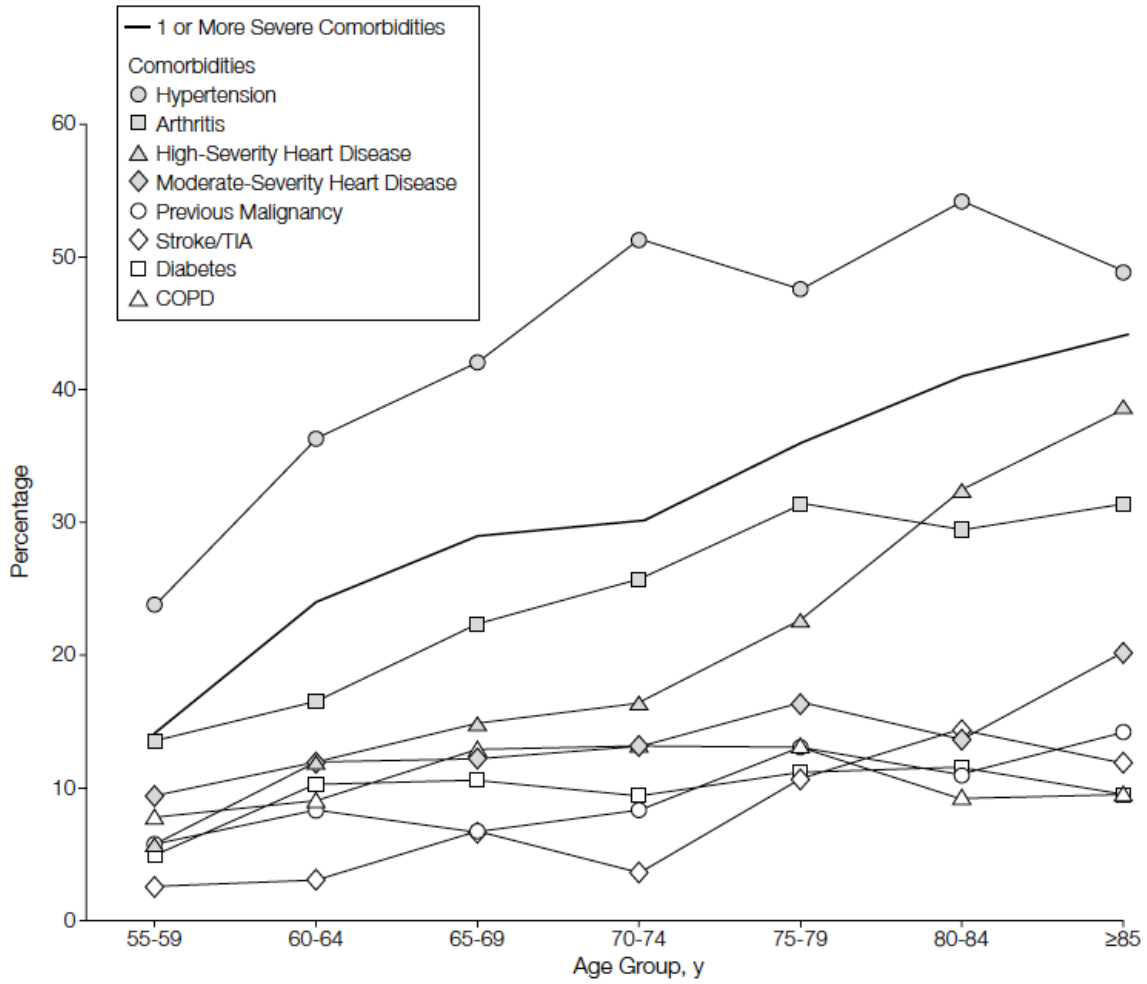
Figure 4. Prevalence and Age Trends by Selected Comorbidities



TIA indicates transient ischemic attack; COPD, chronic obstructive pulmonary disease. All trends were significant at the $P<.05$ level except for diabetes and COPD.

Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older.

Yancik R[1], Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. JAMA. 2001 Feb 21;285(7):885-92.

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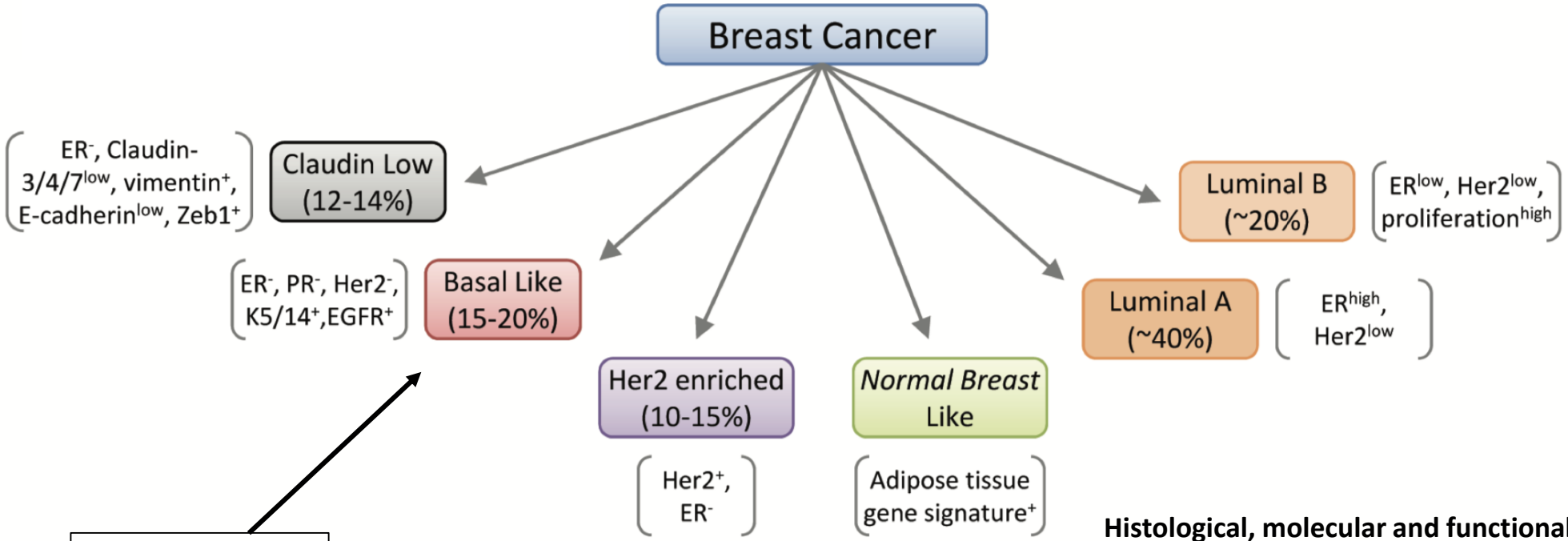
Molecular Classification of Breast Cancers



Triple Negative Breast Cancer (~9% non-basal)

Histological, molecular and functional subtypes of breast cancers,
Gautam K. Malhotra, Xiangshan Zhao, Hamid Band & Vimla Band (2010)
Cancer Biology & Therapy, 10:10, 955-960

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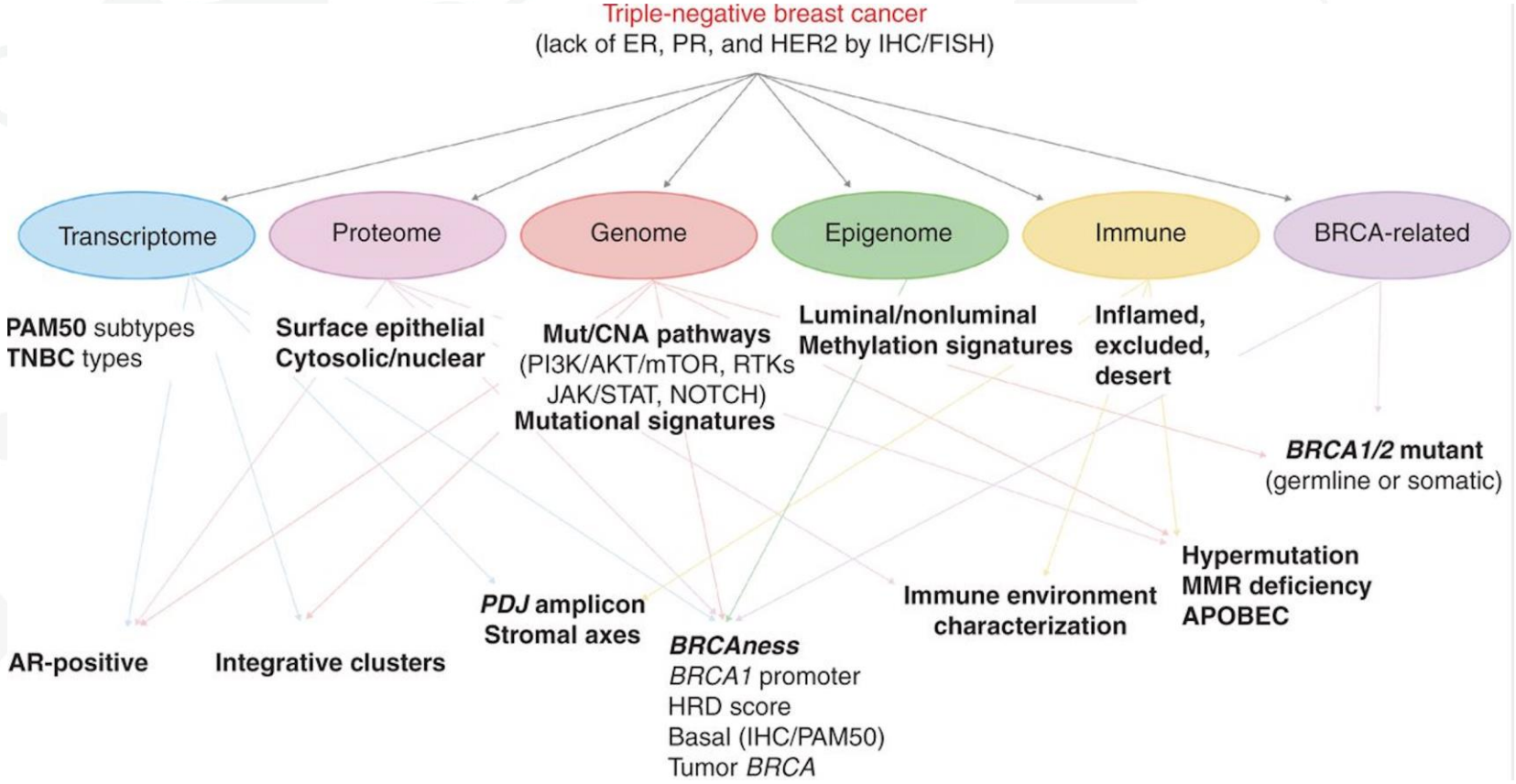
Triple Negative Breast Cancer: TNBC



Insights into Molecular Classifications of Triple-Negative Breast Cancer: Improving Patient Selection for Treatment
Ana C. Garrido-Castro, Nancy U. Lin, and Kornelia Polyak
CANCER DISCOVERY FEBRUARY 2019, p176-198

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Biomarkers/Diagnostics

- Breast Cancer/TNBC Diagnosis
  - Patient management is largely based on ER, PR and HER-2 receptor levels…i.e. diagnosis, stratification and treatment
  - Pathological analysis typically uses IHC and ISH technologies
  - Lack of concordance between IHC and ISH has been observed to be >20% and is grade dependent
  - IHC and ISH do not measure the same biological entity e.g. gene copy # vs protein levels
  - Clinical guidelines and threshold levels are typically not standardized; some countries do have national standard
  - ”Positivity” thresholds range from 1% to 10% or higher
  - Inter-lab/inter-pathologist variability isnotable
  - Analysis of positivity rates in 39 laboratories (33,794 IBC patients) revealed 35.9% (ER), 43.6%(PR) and 28.2%(HER2) outside 95% confidence level
    - **Hormone- and HER2-receptor assessment in 33,046 breast cancer patients: a nationwide comparison of positivity rates between pathology laboratories in the Netherlands,** Carmen van Dooijeweert, Ivette A. G. Deckers, Inge O. Baas, Elsken van der Wal, Paul van Diest**,** February 2019 Breast Cancer Research and Treatment

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Biomarkers/Diagnostics

- Checkpoint Inhibitor Biomarkers
  - PD-L1
    - Heterogeneity in IHC and dependence on specific anti-body used in measurement
    - Lack of standardization for (+) determination
      - **PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics**, Margarita Udall, Maria Rizzo, Juliet Kenny, Jim Doherty, SueAnn Dahm, Paul Robbins and Eric Faulkner, Diagnostic Pathology (2018) 13:12
  - Microsatellite instability
    - PCR vs image-based analysis (sensitivity and specificity)
      - **ESMO recommendations on microsatellite instability testing for immunotherapy in cancer, and its relationship with PD-1/PD-L1 expression and tumour mutational burden: a systematic review-based approach,** C Luchini, F Bibeau, M J L Ligtenberg, N Singh, A Nottegar, T Bosse, R Miller, N Riaz, J -Y Douillard, F Andre, A Scarpa, *Annals of Oncology*, Volume 30, Issue 8, August 2019, Pages 1232–1243
      - **From micrographs to microsatellites in one bold step**, Kamila Naxerova, *Science Translational Medicine* 26 Jun 2019
  - Tumor Mutational Burden
    - Lack of standardization
      - **Implementing TMB measurement in clinical practice: considerations on assay requirements,** Büttner R, Longshore JW, López-Ríos F, et al.. ESMO Open 2019;**4**:e000442.

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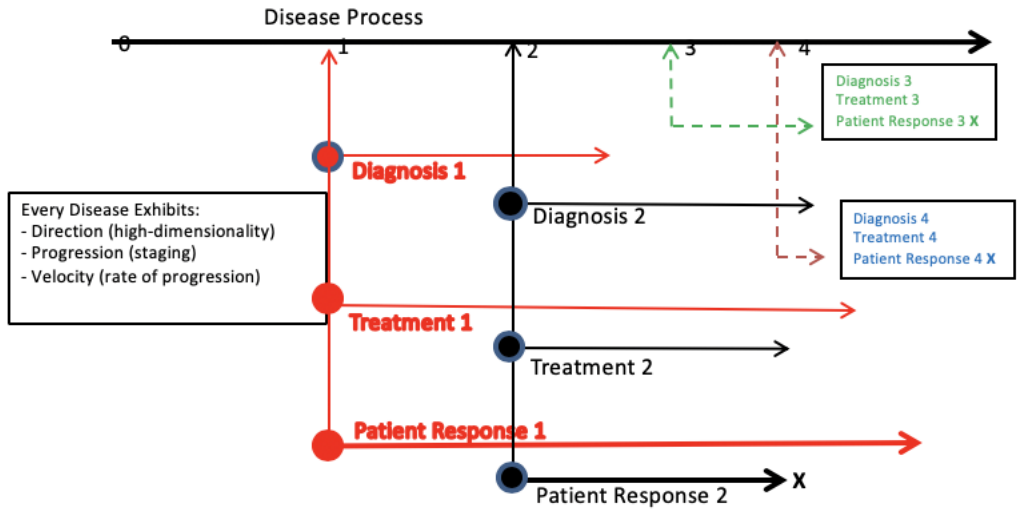
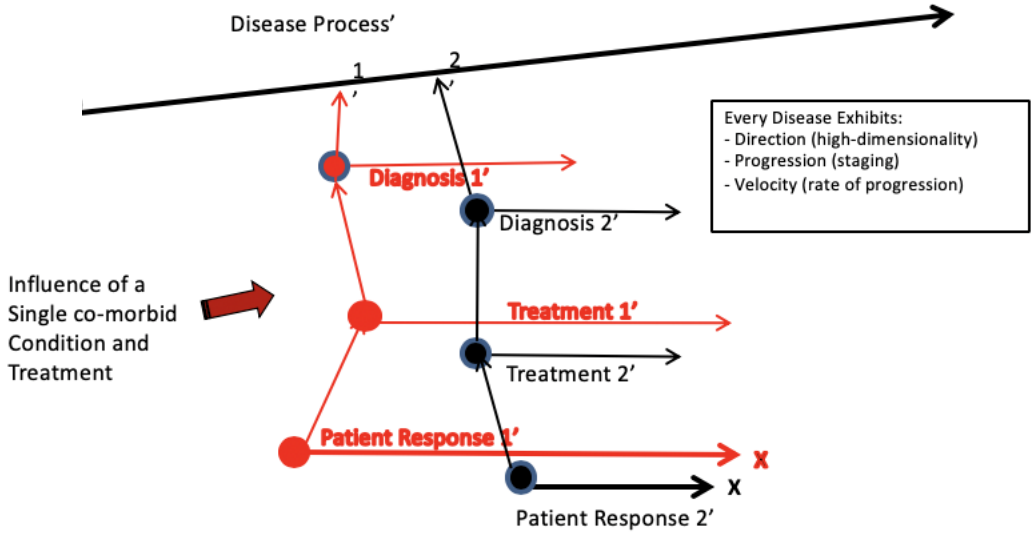
Impact of Co-morbidities and Poly-pharmacy





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Take Home Lessons

- Comorbidities
  - To be expected, especially in middle-age/elderly patients
  - May be ”treated, active”, ”treated, inactive”, un-diagnosed, mis-diagnosed
    - Auto-immune diseases may not be diagnosed for >3 years after initial symptoms
- Poly-pharmacy
  - Always present
    - Not only therapeutics but also OTC’s, dietary supplements, etc
  - Lack of adherence is likely
- Biomarkers
  - Critical for use in diagnosis, prognosis and treatment decisions
  - Thresholds and guidelines are not likely consistent, nationally or internationally
- **Opportunity**
  - **Standardized documentation/annotation of patient history, symptoms and signs can lead to ongoing evolution of better decision support, accurate patient and disease stratification and better patient outcomes and enhance data sharing and analysis=**

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"I think the extreme complexity of medicine has become more than an individual clinician can handle. But not more than teams of clinicians, *researchers and patients* can handle"

Atul Gawande (MNL)