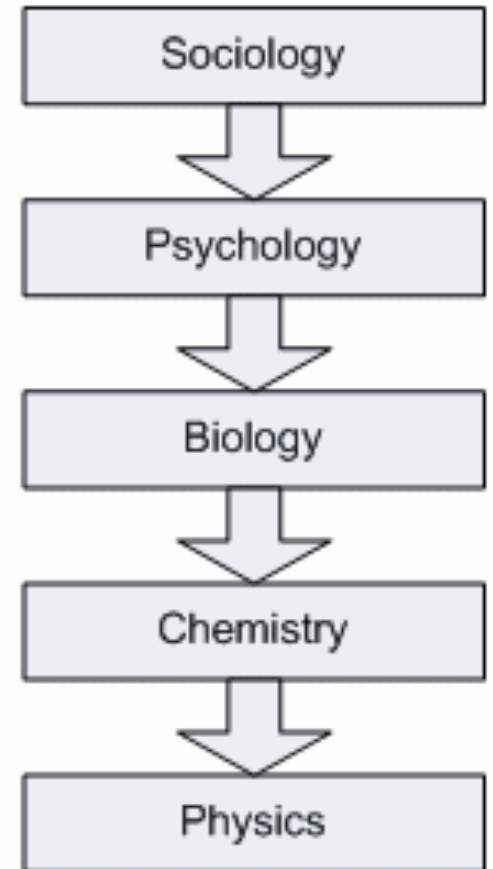


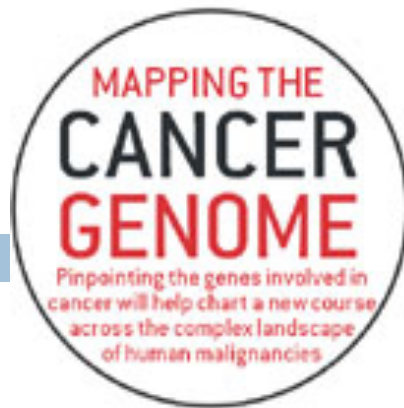
# CANCER: DISUNIFIED KIND, UNIFIED EXPLANATION

# What makes science successful? An intuitive view...

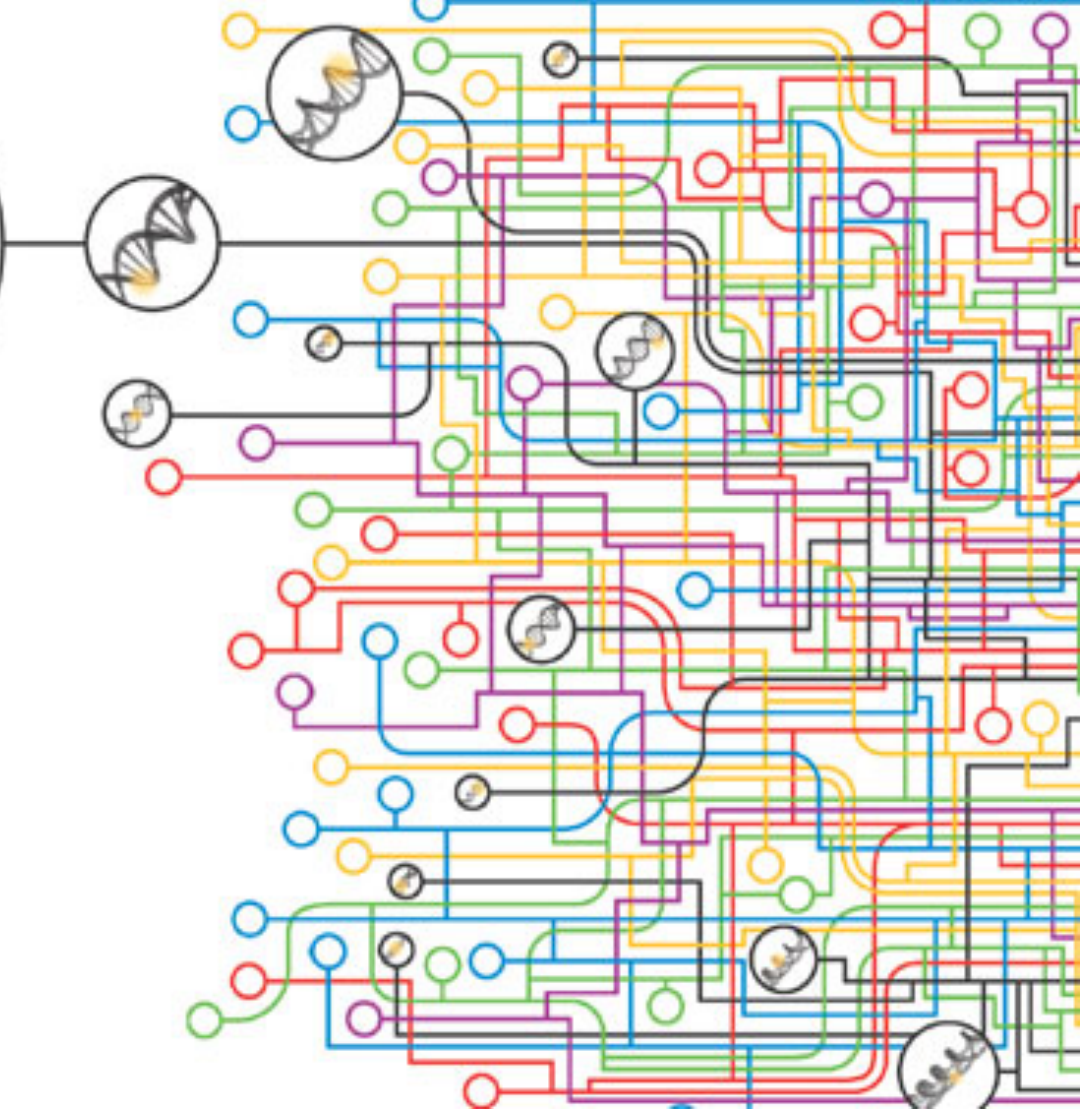
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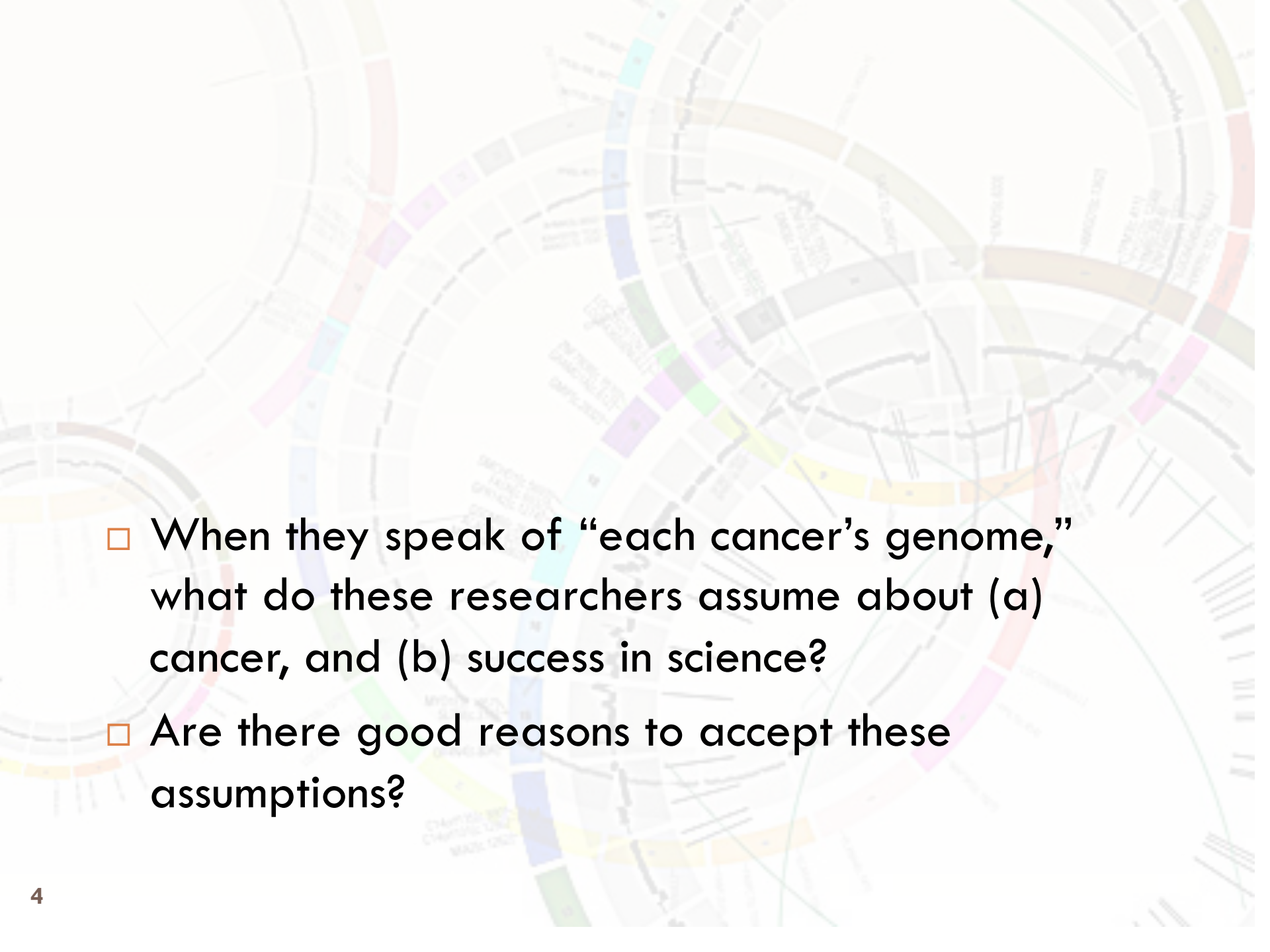
- Successful classification of natural kinds underwrite the reliability of scientific inferential and explanatory practices.
- Natural kinds play an essential role in scientific theories.
- Natural kinds each have a distinctive essence, causal basis or structure, or their properties cluster due to homeostatic mechanisms.
- Kinds are ordered hierarchically, much like the sciences.
- Explanations in science ought to likewise be hierarchically linked.





- “Identifying the changes in **each cancer’s** complete set of **DNA – its genome** – and understanding how such changes interact to drive the disease... to lay the foundation for improving cancer prevention, early detection and treatment...” The Cancer Genome Atlas (TCGA) Program Statement

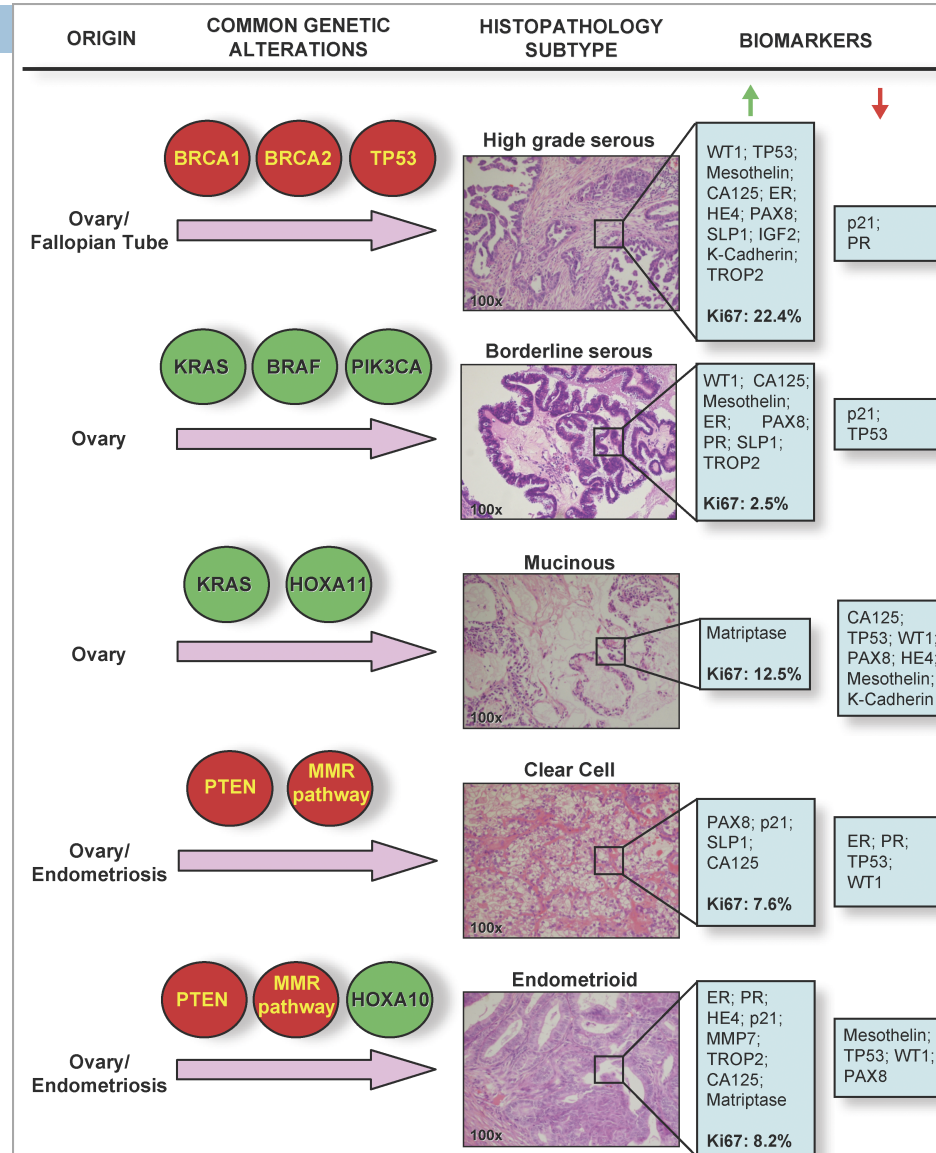


- 
- When they speak of “each cancer’s genome,” what do these researchers assume about (a) cancer, and (b) success in science?
  - Are there good reasons to accept these assumptions?

# Cancer classification is multi-modal

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- Location (e.g., head and neck)
- Tissue of origin (e.g., oral)
- Cell of origin (e.g., squamous cell carcinoma)
- Histopathology subtype (Grades (1, 2, 3), tissue/cell sub-type)
- Stages ( $\neq$  Grades!) (e.g., 0, I, IA, II, IIA, local, advanced, etc.)
- Common genetic alterations
- Biomarkers, gene expression profiles, epigenetic profiles
- Remote etiology: e.g., “infectious” cancers



- What kind of cancer did you have?
- Lung.
- Ok, but what kind of cancer did you have?
- Small Cell carcinoma
- Ok, but what kind of cancer did you have?
- Mildly differentiated, I think Grade 2.
- Ok, but what kind of cancer did you have?
- Stage 2.
- ...



# Classifications & their functions

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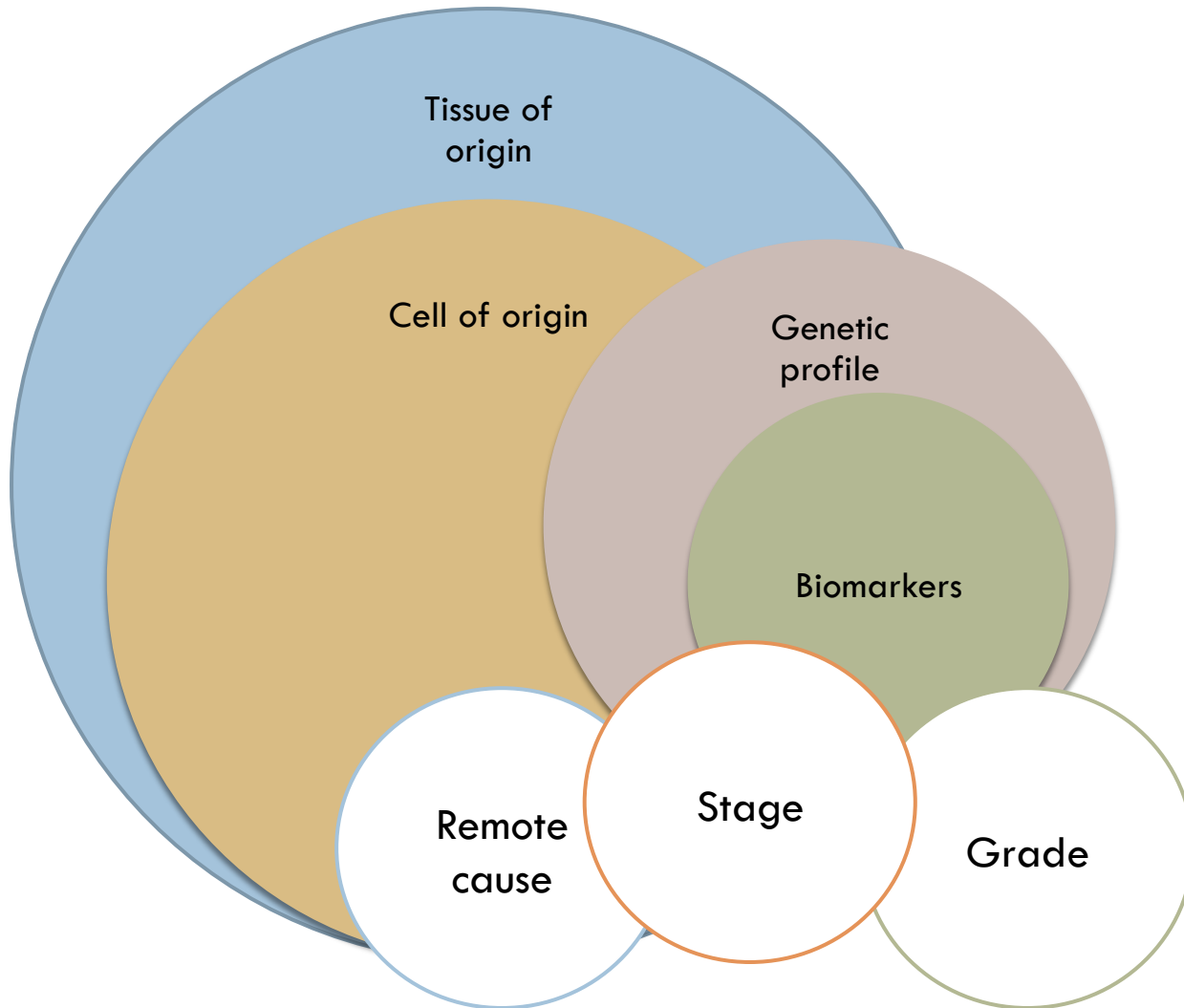
## Mode of classification

- “Clinicopathological”:
  - Stage
  - Grade
  - Sex, age, family history, remote causes
- “Molecular”:
  - Biomarkers
  - Typical genes altered, or typical molecular pathways, whole genomic profile, proteomics, transcriptomics, etc.

## Functional role

- Diagnostic/prognostic, treatment relevant
- Mechanistic understanding, potential for treatment relevance

# Cross cutting classifications

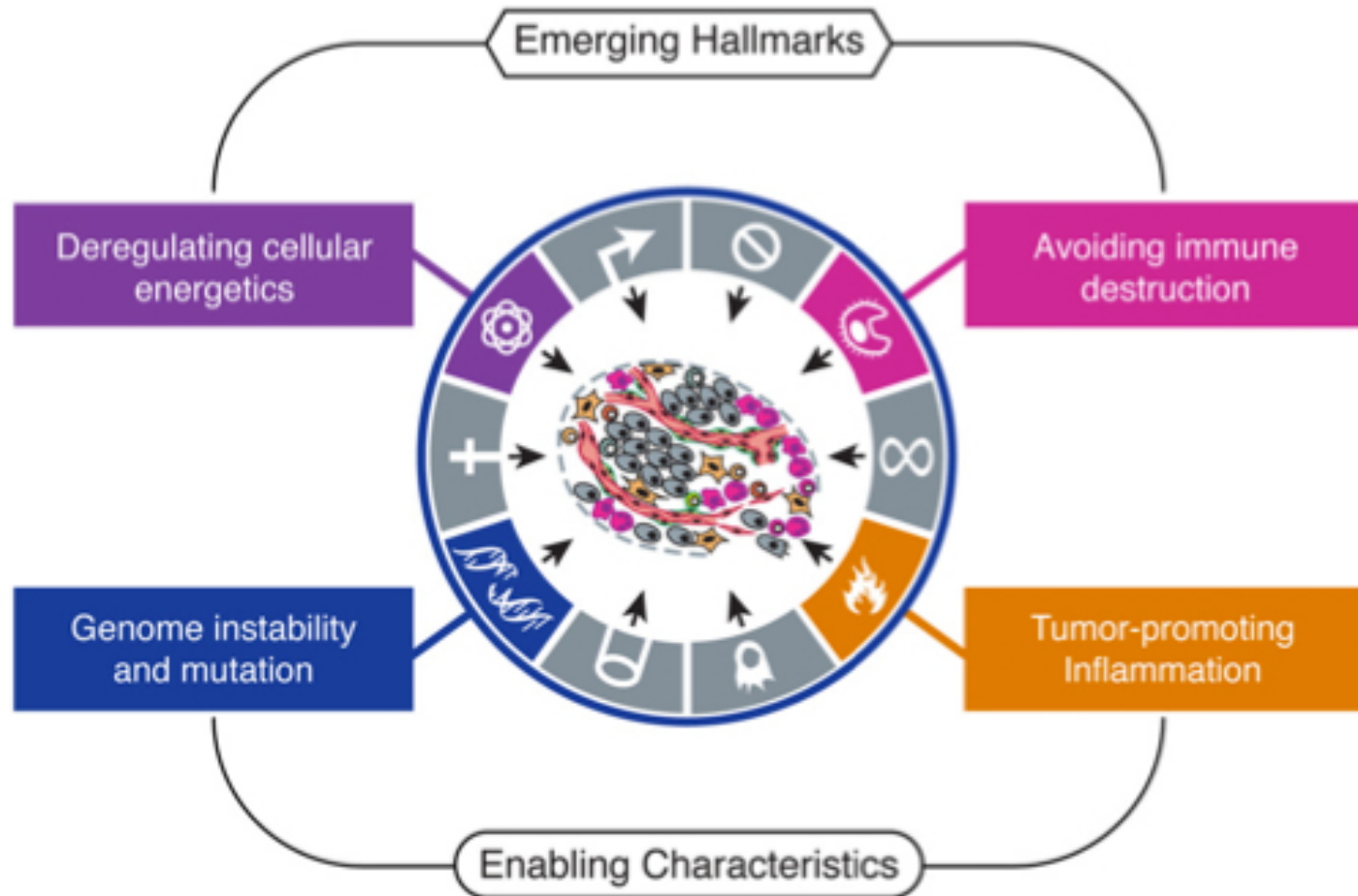




# Why is cancer classification so complicated?

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- The “same” type of cancer (in the sense of tissue of origin) in different patients may have different prognoses, due to different stage or grade, sex and/or age of patient, history of infection, etc.
- How any particular cancer behaves has to do not only with cell intrinsic features but also with cell-extrinsic features. The same mutations have different effects, depending on when & where they arise.



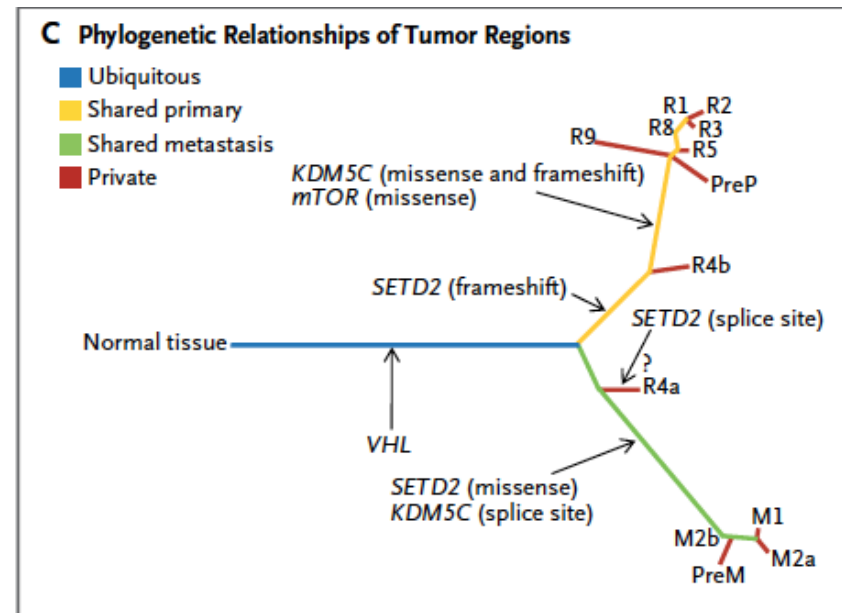
“... the biology of tumors can no longer be understood simply by enumerating the traits of the cancer cells but **instead must encompass the contributions of the “tumor microenvironment” to tumorigenesis.**” Hanahan and Weinberg. 2011. “Hallmarks of cancer: the next generation.” *Cell*. 144(5): 646-74.

# One last stinker...

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- Cancer progression is a process. Cancers are evolving population with dynamic properties.
- Each cancer is genetically unique: “...the combination of drivers within a cancer type and their distribution within the founding clone and subclones varies for individual patients. This suggests that knowing the clonal architecture of each patient’s tumor will be crucial for optimizing their treatment.” (Kadroth, et. al. 2009)

Gerlinger, et. al. 2012. “Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing.” NEJM. 366: 883-892.



# The upshot

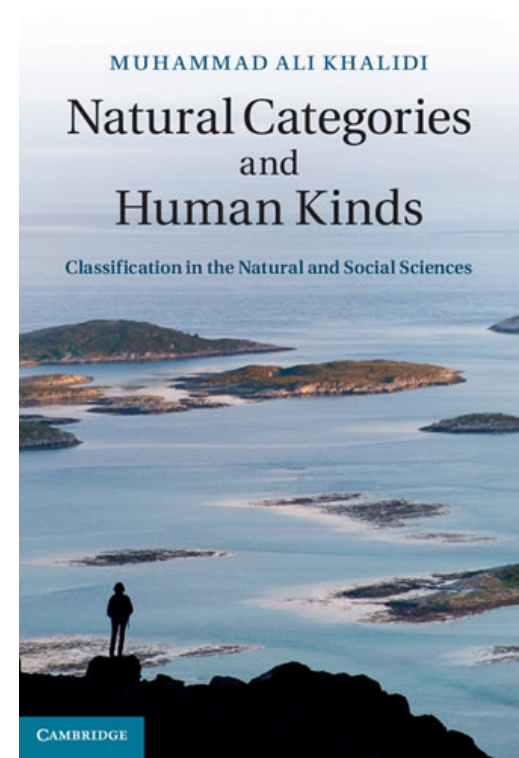
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- There are diverse cross-cutting ways of classifying cancers, which serve different purposes, in virtue of their identification of different features.
- The hope for a definitive nosology of cancer founded on genomics alone *assumes that mutations are the distinctive causal factors in cancer*, an assumption proving difficult to sustain in the face of empirical evidence.
- No single mechanism underlies cancer progression. Complex phenomena such as cancer may require a different picture of both (a) kinds & their classification, and (b) progress in science.

# Khalidi on Cancer as a Kind

## □ Khalidi:

- **“the kind of entity that is most closely implicated with the process of cancer is cancer cell. I will argue that once the cancer cell is understood as a natural kind of entity, then cancer can be seen as a natural kind of process... Of all the natural kinds we have looked at this is perhaps the one most in line with Boyd’s homeostatic property cluster account. ... the mutated caretaker genes can be thought of as the causal mechanism...”**



# Khalidi: Essentialist?

- Cancer cells' causal properties are only **one** (of many) necessary conditions on cancer progression, metastasis in particular.

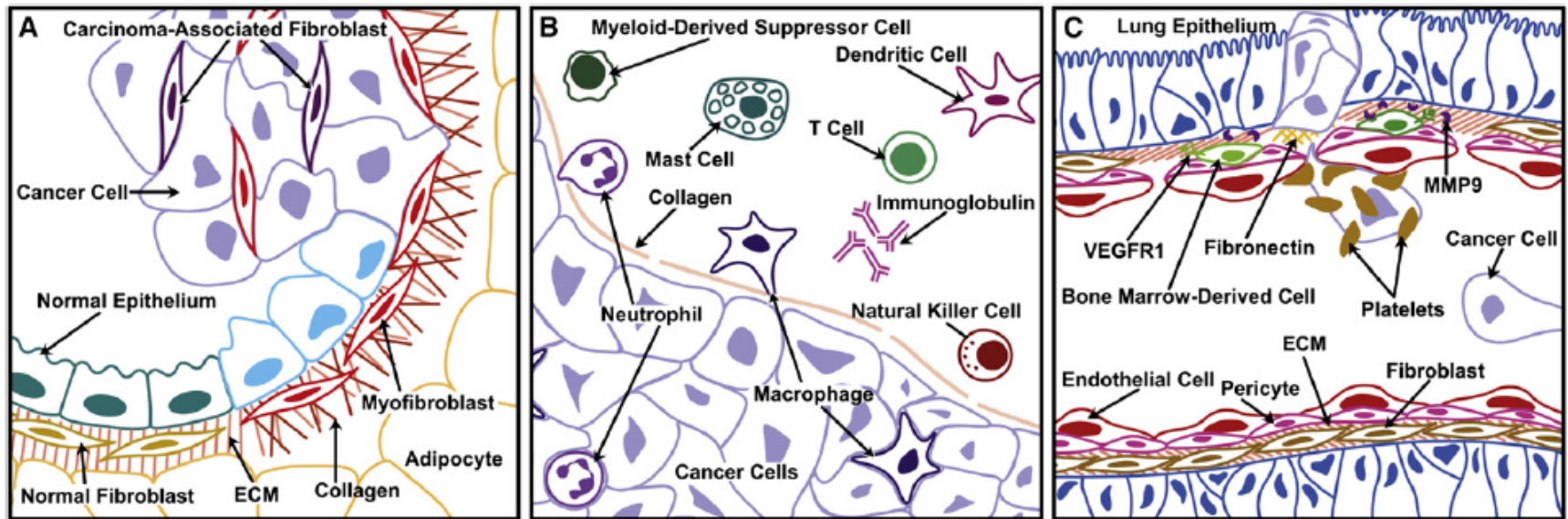
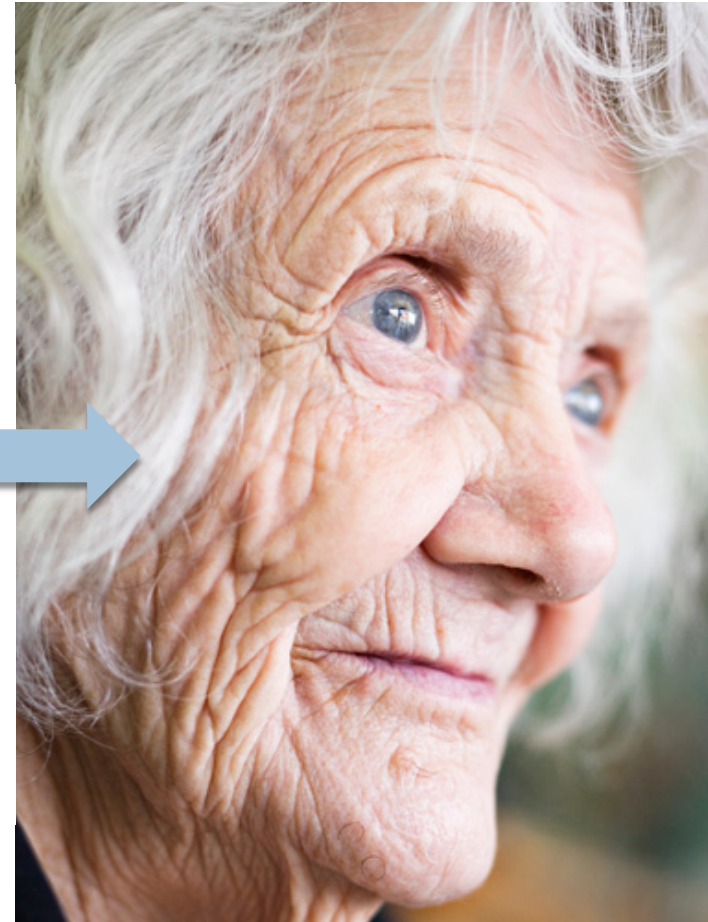
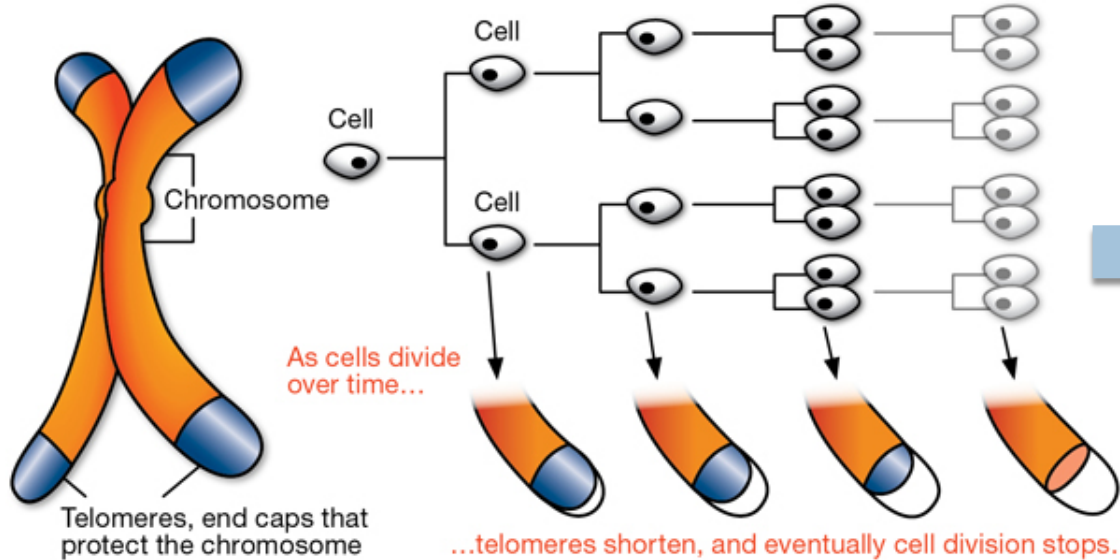


Figure 2. Interactions between Cancer Cells and Stromal Components Influence Tumor Growth and Progression

Egeblad, M., Nakasone, E.S., and Werb, Z. (2010). Tumors as organs: complex tissues that interface with the entire organism. *Dev. Cell* 18, 884–901.

# An analogy: Aging

## Telomere Shortening



# Dimensions of complexity of causal process → disease

- Single initiator
  - Single pathway
  - Extent of interaction both w/in pathway, & w/ genes, environment
  - Extent of increase in interaction over the course of the disease process
- Multiple initiators
  - Multiple pathways
  - Extent of interactions across pathways, w/ genes, environment
  - Extent of increase of interaction over the course of the disease process

Infectious disease

Arthritis

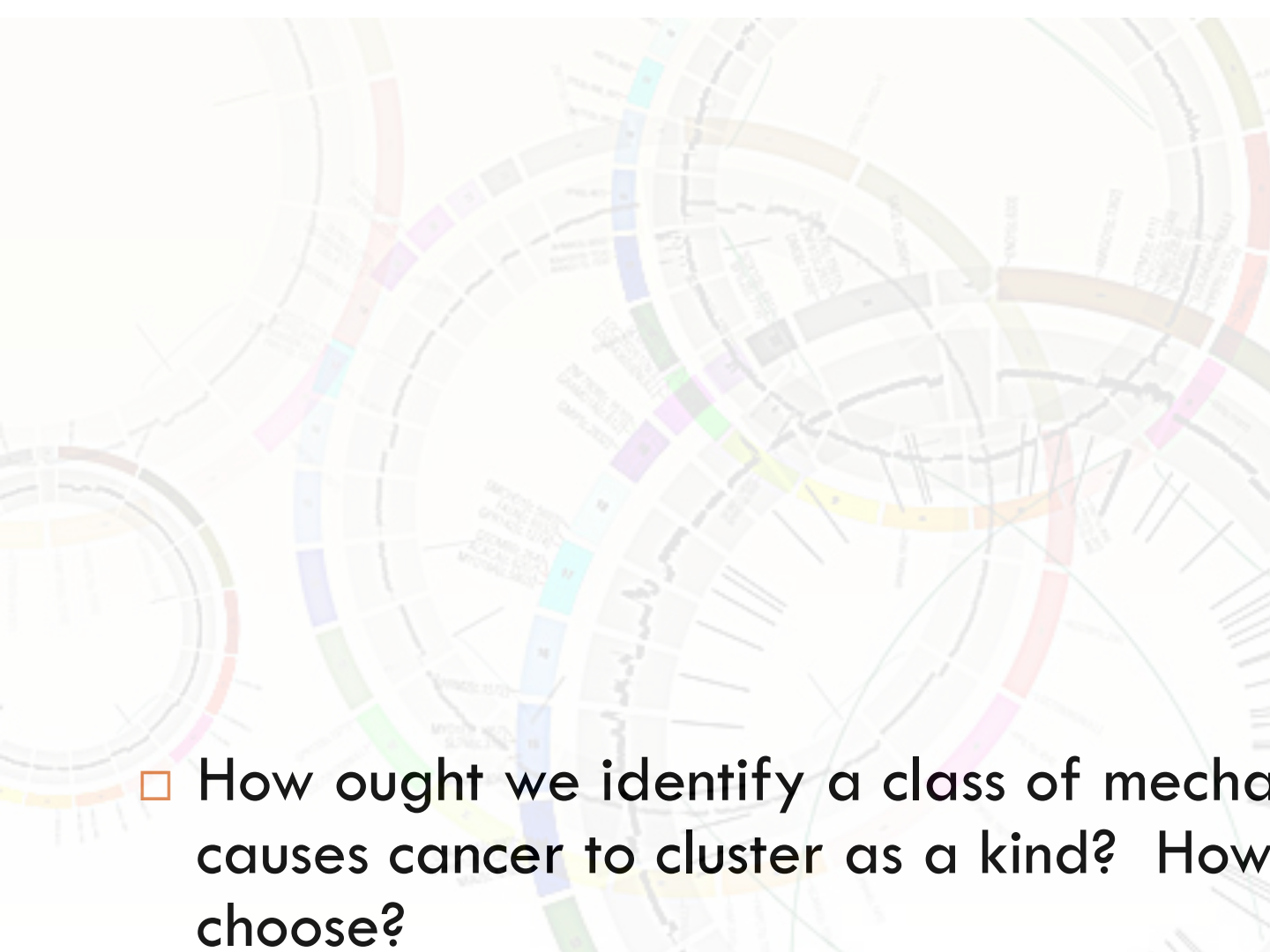
Cancer

Depression

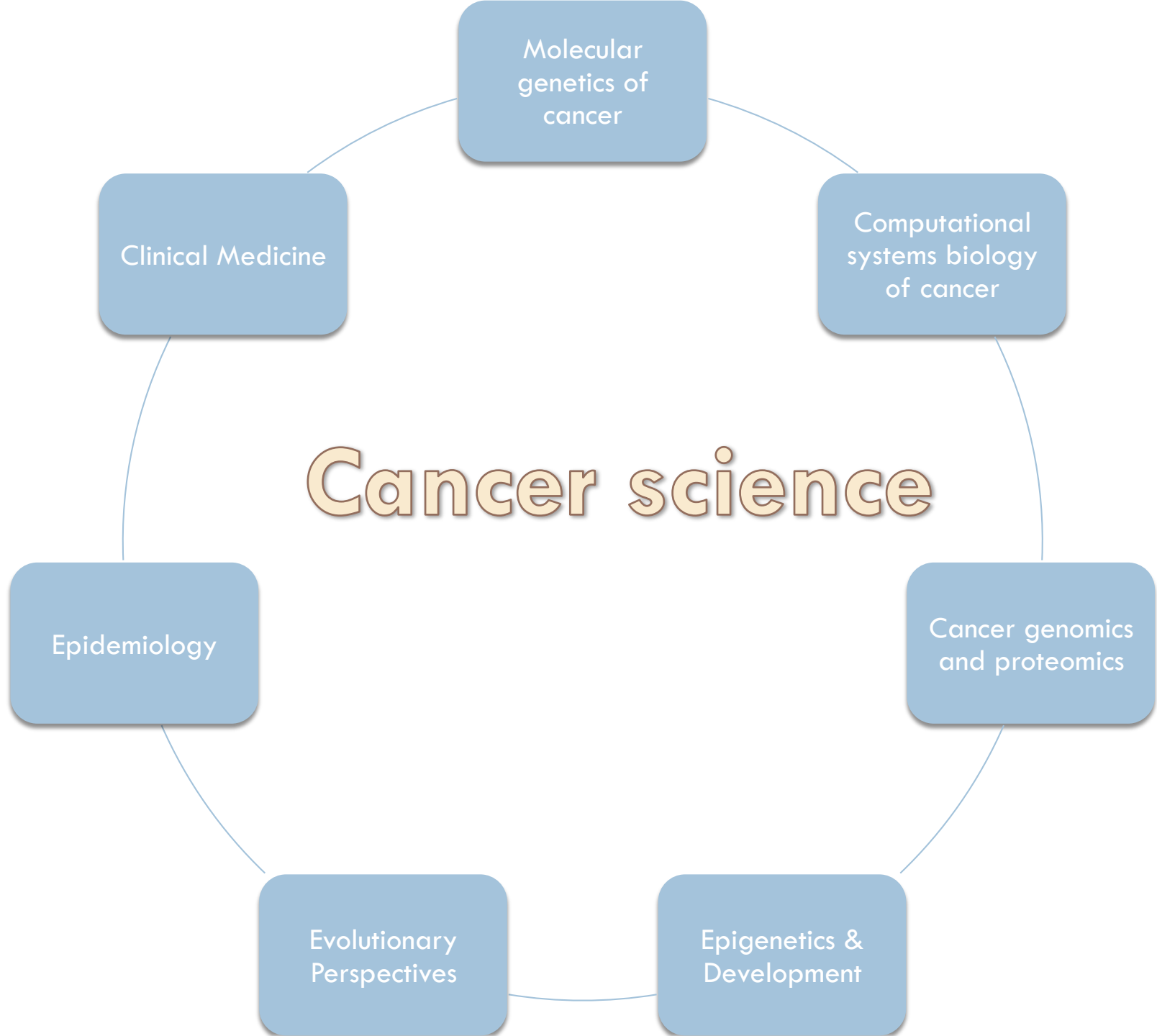
Aging







- How ought we identify a class of mechanisms that causes cancer to cluster as a kind? How do we choose?
- Do we need a new picture of scientific success? What should it look like?



## □ Cancer

- ✓ Heterogeneous
- ✓ Different disciplinary approaches, questions
- ✓ Different methodologies
- ✓ Target explananda operationalized differently
- ✓ Disciplines parse causal space differently
- ✓ Integrative theories?

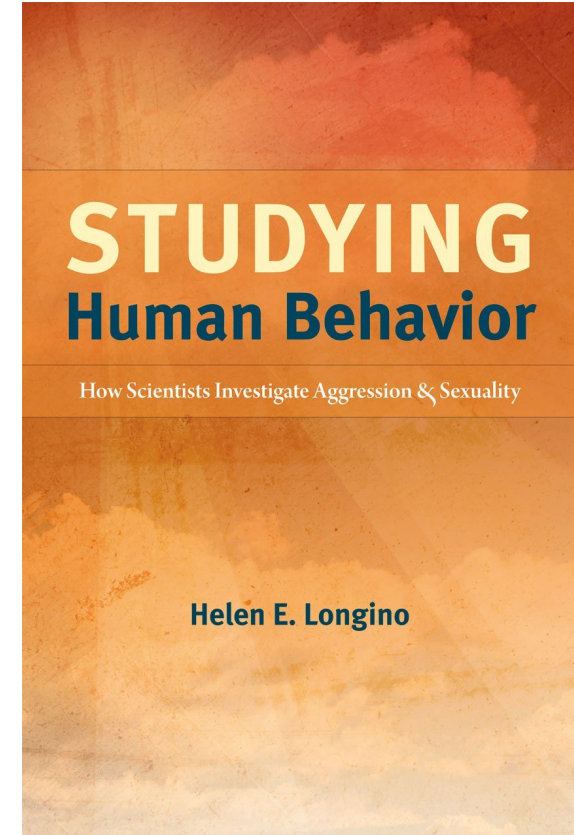
## □ Aggression/Sexuality

- ✓ Diffuse Target
- ✓ Different disciplinary approaches, questions
- ✓ Different methodologies
- ✓ Same(?) phenomena operationalized differently
- ✓ Disciplines parse causal space differently

# Longino's view:

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- “From an empirical point of view, what we know is piecemeal and plural. **Each approach offers partial knowledge** of behavioral processes gleaned by application of its investigative tools. In applying these tools, the **overall domain is parsed so that effects and their potential causes are represented in incommensurable ways**. We can (and do) know a great deal, but what we know is not expressible in one single theoretical framework...we may remain metaphysically committed to the view that multiple factors or processes **are interacting in our one world.**” (Longino, 2013, pp. 144-7)



# Uncomfortable resting point?

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- “This is an uncomfortable resting point. Longino has **argued for the continuing importance of multiple, incommensurable approaches, and yet urges greater interaction among those same approaches.** Incommensurability suggests inability for one approach to speak to another, and on the other hand, interaction among approaches suggests the integration that Longino dismisses.”  
Potochnik, NDPR

# Pluralism + Integration ?

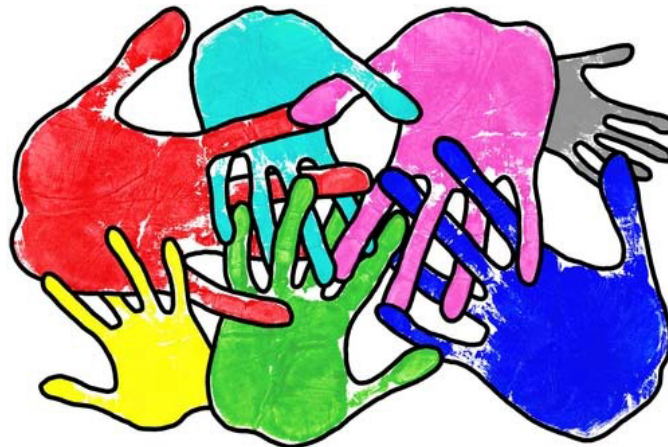
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- What is it to be a “pluralist”?
- When/why ought we to embrace pluralism about scientific taxonomy, methods, or theories?
- Can we consistently embrace a pluralist view, and see (at least part) of scientific progress as involving greater interaction, or “integration”?
- What is productive interaction? When are integrations “successful”? When and how do they fail?

# Pluralism

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- “... inquiry may sustain a multiplicity of viable approaches, each generating some knowledge. The question becomes not which one is best or better, but what each contributes – both in terms of our positive results, and in terms of critical perspectives on the others – to our overall understanding of the phenomenon. This openness to plurality of approaches constitutes philosophical pluralism.” (Longino, 2013, p. 2)



# Pluralisms

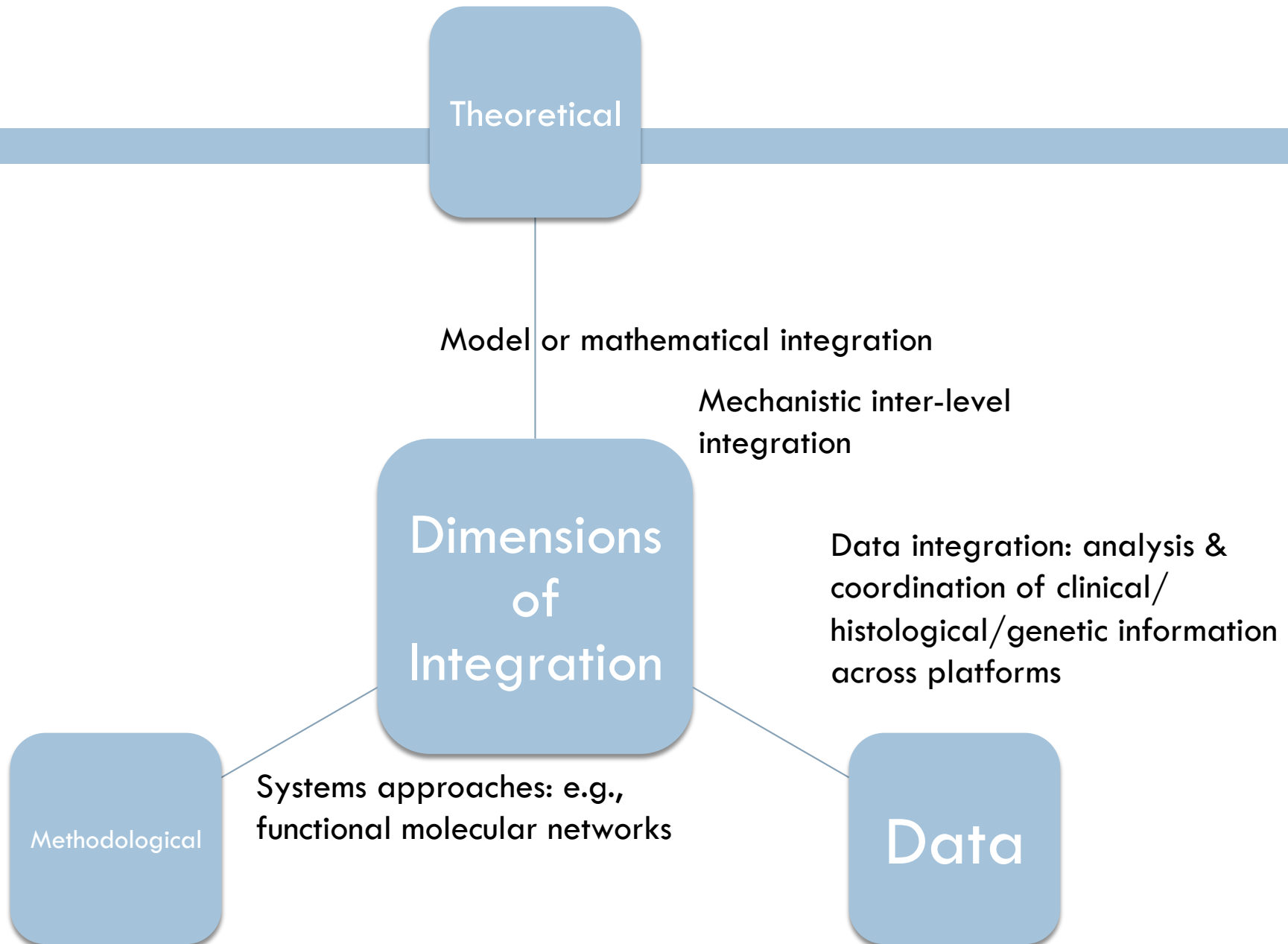
- **Methodological:** a variety of methods or disciplinary approaches, at least initially, may be worth pursuing independently.
- **Epistemic:** “natural phenomena *cannot be fully explained* by a single theory or fully investigated using a single approach.... multiple approaches are required for the explanation and investigation of such phenomena.” (Kellert, et. al. 2006)
- **Metaphysical:** the world is “dappled” (Cartwright 1999).
  - ▣ (1) Laws of limited scope form a loose patchwork rather than reducing to a compact, unified set of fundamental laws.
  - ▣ (2) Alternatively, “promiscuous realism”: diversity of possible classifications of kinds. (Dupré, 1993)



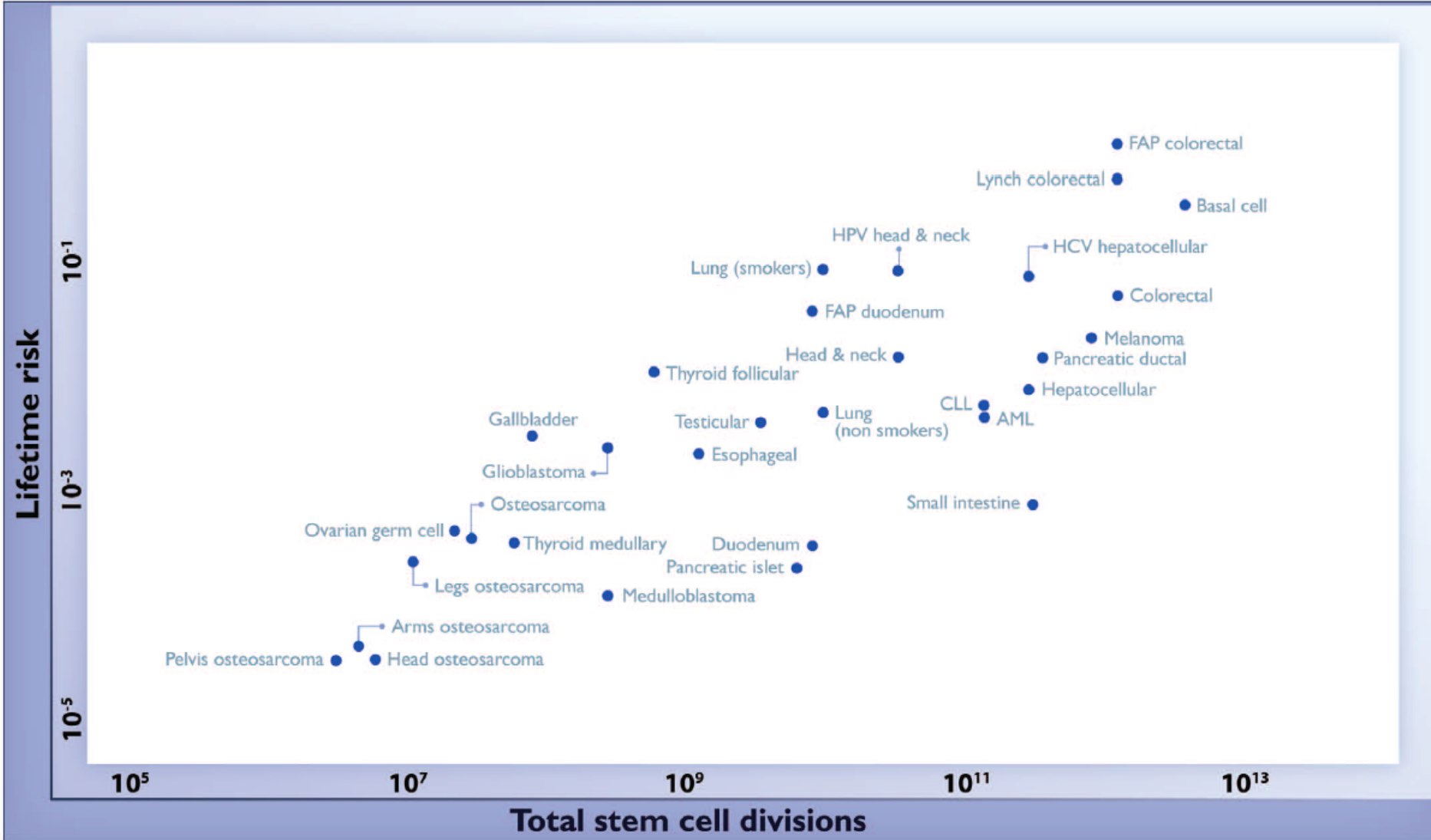
# My view:

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- **Methodological:** unproblematic.
- **Epistemic:** Different *aspects* of the same phenomenon may require different explanations. Success is piecemeal and multifaceted, in part due to diverse predictive and explanatory goals. General theories can explain large classes of phenomena, but explanatory scope is often at the cost of precision. “Integrative” approaches vary.
- **Metaphysical:** There is one world, but legitimate cross-cutting classifications.



Tomasetti, et. al. 2014. "Variation in cancer risk can be explained by the number of stem cell divisions. Science. 347: 6217. pp. 78-81.



FAP = Familial Adenomatous Polyposis ♦ HCV = Hepatitis C virus ♦ HPV = Human papillomavirus ♦ CLL = Chronic lymphocytic leukemia ♦ AML = Acute myeloid leukemia

**Fig. 1. The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue.** Values are from table S1, the derivation of which is discussed in the supplementary materials.

# A “unified” explanation

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- Tomasetti & Vogelstein, (2014) “only a third of the variation in cancer risk *among tissues* is attributable to environmental factors or inherited predispositions. The majority is due to “bad luck,” that is, random mutations arising during DNA replication in normal, noncancerous stem cells.” (Assumes somewhat artificial partitioning of causes.)
- The argument
  - Cells divide.
  - Mutations happen.
  - Some tissues have more stem cell divisions than others.
  - Cells that divide more often have more mutations.
  - Tissues with more stem cell divisions & more mutations are more frequently subject to cancers.
  - QED

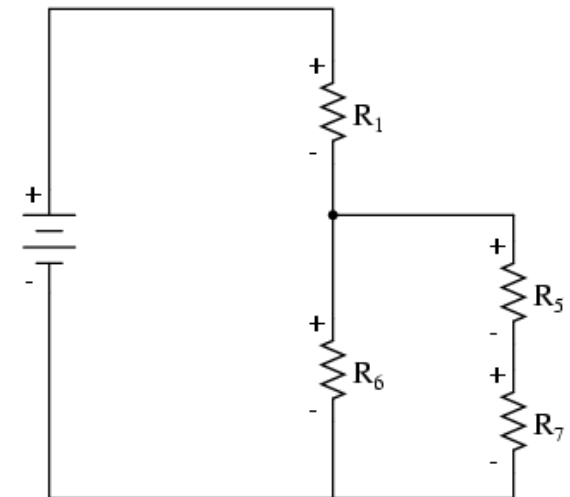
# (VERY) Local mechanistic integration

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- Typical pattern of (80%?) of molecular genetic research on cancer:
  - ▣ X gene is found commonly mutated in cancer Y.
  - ▣ X gene is associated with function F.
  - ▣ Function f is associated with pathway P.
  - ▣ Pathway P affects downstream expression of genes A, B, and C, and/or epigenetics of gene expression, etc..
  - ▣ Genes A, B, and C, when mutated or differentially expressed, can cause one of the typical hallmarks of cancer cells: chromosomal duplication, dedifferentiation, cell cycle disruption, can desensitize the cell to apoptotic signaling, etc.
  - ▣ X gene is found to be differentially expressed in mice, yielding distinctive pathology.
  - ▣ “In conclusion, we have identified a novel tumor-promoting mechanism...”

# Mechanistic explanations in context

- Diagrams of cell regulatory pathways bear a striking resemblance to circuit diagrams.
- Nodes in these pathways play functional roles akin to those in a circuit. Some nodes “interrupt” the flow of information; these are analogous to switches that are “open” in that they “block” or “inhibit” activity, or the continued production of a signal.
- Other nodes serve as “resistors”; they “do work” with the information – usually by directing the signal to activate another pathway, which may in turn either induce transcription of a gene, or “upregulate” a protein.

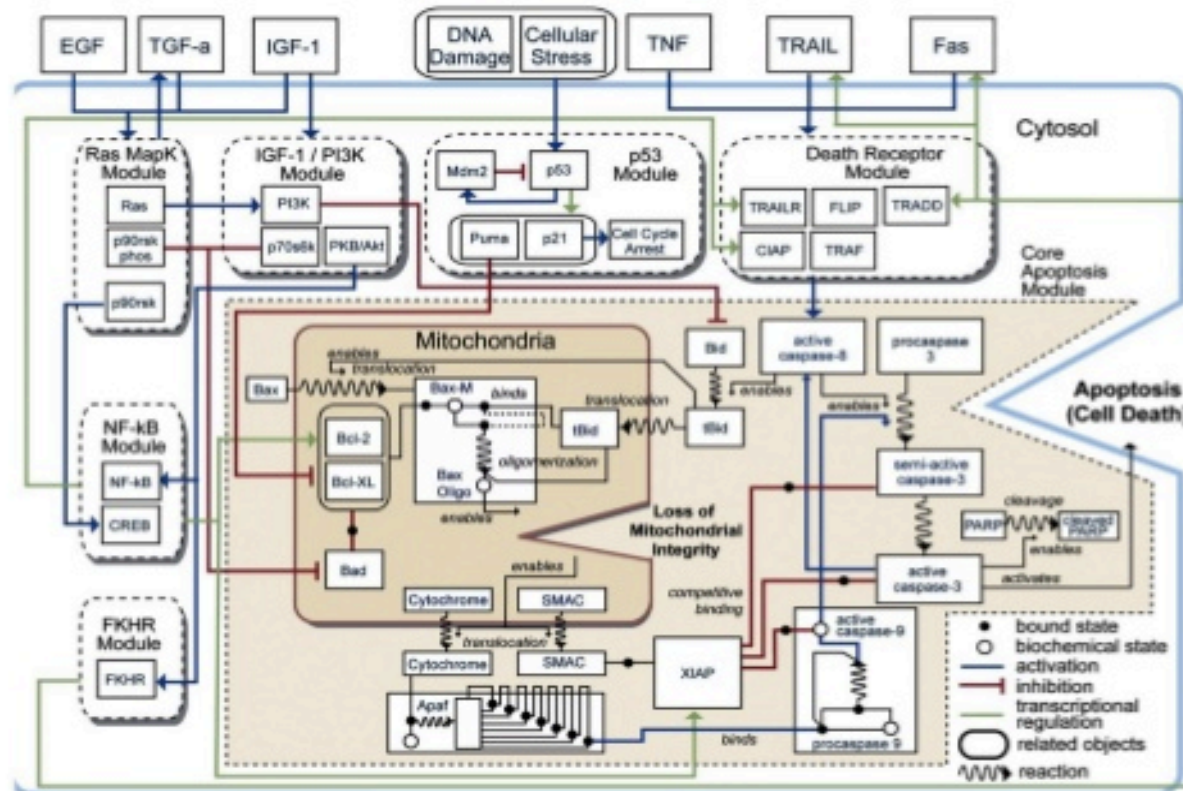


A series circuit

# p53: “Master Guardian and Executioner”

## Weinberg 2014

### The Apoptotic Circuit Board



The full array of components governing apoptosis is not known. An initial attempt at modeling the system is shown.

# Cell signaling pathway $\neq$ ? circuit

- Activated by “floating intervenors”: external signals with more or less specificity (e.g., “IGF-1,” “cyclins,” “ligands,” “mitogens,” “DNA damage,” or “Cellular stress”)
- No “closed” circuits in the cell.
- Multiple “inputs,” and “endpoints.” That is, the same elements may play a variety of functional roles in distinct regulatory pathways.
- Same pathway may be deployed to different ends, drawing in different elements at different stages in development or the life cycle of a cell.
- Many pathways are often operating simultaneously and co-regulate one another.



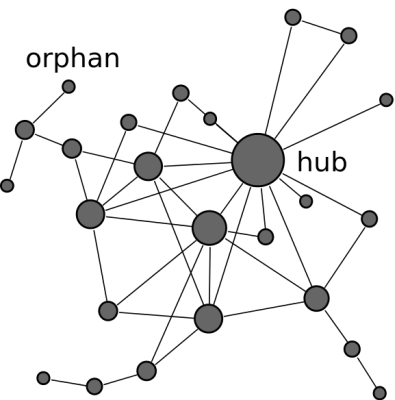
# Limits of Mechanistic Decomposition

- Cells divide or fail to divide in response to intra- and intercellular signaling pathways, pathways that extend far beyond the cell.
- Mechanistic explanations of subcellular pathways in cancer thus have this core limitation: they are always characterizations of only **one pragmatically bounded subset of a wider system of regulatory controls on cell division.**
- Evolution has designed this redundancy exactly because break down in one element will call upon regulatory controls in other signaling pathways.

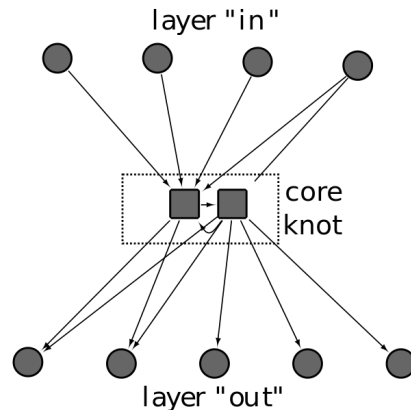
# Robustness

- What cancer illuminates is how systems subject to multiple sources of breakdown find stable solutions, **or how robustness evolves.**
- **Indeed, cancer itself can be viewed as the evolution of a robust system: a network with its own cooperative functional organization, that continues to perform its function despite variations in environment and organization...**

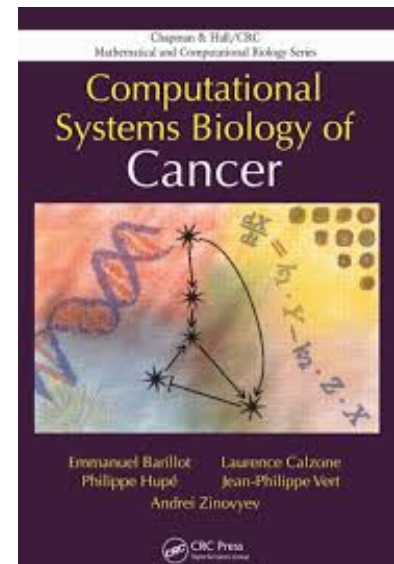
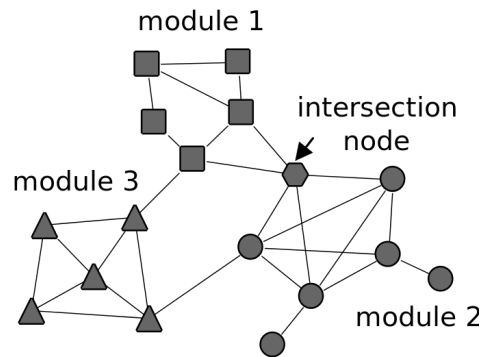
(A) scale-freeness



(B) bowtiness

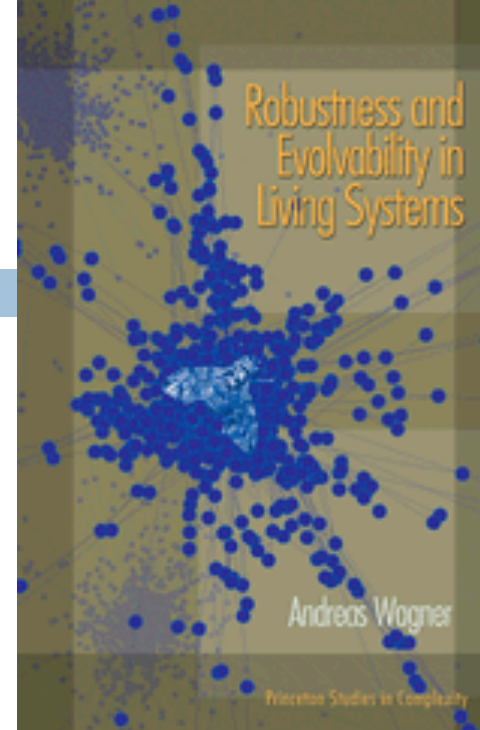


(C) modularity



# Conservation & Evolvability

- There's a tension in evolution, however, between **conservation of entrenched structures (robust structures)**, and **quasi-independence of parts**.
- Wimsatt and Schank (drawing upon H. Simon, 1967) say this leads to the “GE paradox”



# The GE Paradox

- The paradox is that there are fitness advantages due to entrenchment, and fitness advantages to modularity, but the two cannot be achieved simultaneously:
- “Modularity, duplication, and functional redundancy should each *decrease* entrenchment by reducing interdependence between or dependency upon specific system components.”



# Victims of our own success?

- Arguably, cancer is in some ways a product AND byproduct of both entrenched elements (or, scale free networks; like the functional centrality of p53), AND, modularity: the capacity for parts to vary independently without affecting the whole: two features that contribute to **robustness**.
- Modularity makes it possible for a tumor (or, its components – subpopulations of cells) to develop gradually in a specific organ without necessarily affecting the the organism as a whole, which is why many tumors are not discovered until it is too late. I.e., cancer coopts the very same features (modularity, plasticity, robustness) that makes us so highly evolvable as a lineage. We are a victims of our own success.

# Interlevel integration? No, here's why:

- Failure of **the same** mechanism can occur in **different ways**, or in the **same way**, with **different effects in different cancers**. In fact, this is what cancer researchers have come to expect.
- I.e., it's mistaken to think that integration or explanation and thus subtype classification in complex systems is "complete" when we identify 'the' mechanism, because (a) there is not one, and (b) the same "mechanism" (or failure of mechanism) will have different effects across different genetic and epigenetic backgrounds.

# Conclusions

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- There can be no classification of cancer that hierarchically subsumes each subtype in light of genomic features alone.
- Nonetheless, cancer science is predictive and explanatory.
- Success is piecemeal: due to diverse predictive and explanatory goals, and the massive heterogeneity & complexity of cancer, as well as its evolutionary dynamics.
- There are general theories (with wide scope but little precision or predictive power), and local integrative explanations.
- Integration can come in different varieties. Scope trades off with predictive power. Interlevel “mechanistic” explanation is of little relevance in complex systems with robustness & evolutionary dynamics.



Extra slides



# Cancer a unified kind?

- There is no essence shared all and only with cancer, nor a single causal basis. Nonetheless, there are common features:
  - ▣ incidence (by and large) rises with age
  - ▣ more common in tissues with high rates of turnover of cells
  - ▣ involves differentiation (arrest in or dedifferentiation)
  - ▣ involves incapacity to regulate cellular growth
  - ▣ all and only in metazoans (organisms with a mesoderm and the capacity to EMT (i.e., byproduct of modularity, plasticity)
  - ▣ evolutionary process
  - ▣ cancer **cells** have “typical” capacities: resistance of apoptosis, loss of control of cell division, acquisition of a blood supply, many associated with mutations affecting the cell cycle.

# Kinds of kinds

- **Essentialism:** members of a natural kind share a real essence
- **Causal theories:** natural kinds are groups of individuals with shared properties that cluster in virtue of a common cause or mutually stabilizing “homeostatic mechanisms” (i.e., ‘homeostatic property clusters’)
- **Functional kinds:** kinds whose characteristic similarities must consist only in the activities, processes, or roles that category members perform.
- **Stable Property Cluster kinds:** when a cluster of properties is “sufficiently stably coinstantiated to accommodate the inferential and explanatory uses to which particular sciences put such categories.”

# Lange, the “end of disease”? (2007)

- Disease as “incapacity” to regulate some function.
- [Cancer]...is the incapacity to regulate the growth and reproduction of certain cells. But this incapacity, though unifying all cancer, is rather vague because the proper regulation of cell growth and reproduction is achieved by a combination of many separate capacities, each of which must be disabled in some (perhaps independent) way for a tumor to form and to metastasize... Although they might all be lumped together as constituting a single incapacity (to regulate cell growth and reproduction), this incapacity is not especially unitary... It might better be described as a conjunction of various incapacities... (Lange, 2007, p. 284)

# “(Dys)functional” kind?

- But, (a) other diseases involve dysregulation of cellular growth...
- And, (b) what **system** does cancer compromise the function of...?
- A single cell, a population of cells, an organ, or the body as a whole?
- Where we target our analysis of function will shift as we move from asymptomatic cancers to more advanced cases.

# Generative Entrenchment

- Wimsatt and Schank (2004): “a dynamic structural feature” of certain kinds of “generative structures.”

The generative structure of a system:

- ▣ ...has a characteristic set of causal interactions which could be variously represented. One of the simplest representations is a directed graph, where nodes are parts, processes, or events, and arrows are consequences of the presence or operation of nodes on other nodes. For each node, consider how many other nodes can be reached from it by following the arrows. This indicates how much of the phenotype is downstream of, causally dependent upon, or affected by a given node. We define the generative entrenchment (GE) of a node as the magnitude of its downstream dependency...

# COMMENT

## What are the hallmarks of cancer?

The seminal article by Douglas Hanahan and Robert Weinberg on the hallmarks of cancer is 10 years old this year and its contribution to how we see cancer has been substantial. But, in embracing this view, have we lost sight of what makes cancer cancer?

- Lazebnik (2010) noted: *benign tumors share 5 of the 6 properties: sustained angiogenesis, evasion of cell death and insensitivity to antigrowth signals, limitless replicative potential, self-sufficiency in growth signalling... ONLY tissue invasion and metastasis distinguishes cancerous tumors...*
- “after producing nearly two million papers on cancer, we are yet to **learn the underlying mechanisms sufficiently well to have a sizable impact on cancer mortality**. Otherwise... with the war on cancer about to enter its fifth decade, we might keep winning the battles, but losing the war.” (Lazebnik, 2010)

# Patchwork taxonomy?

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- “The image of the scientific enterprise that emerges from these considerations is of a patchwork of overlapping theories or taxonomies, some of which inquire into different spatiotemporal levels, whereas others inquire into the same level relative to different interests. It is futile to look for a single system of categories that uniquely classifies a certain set of phenomena. *For any given spatiotemporal level, there does not seem to be a limit on the number of taxonomic systems that may categorize it, so uniqueness is not a promising construal of what makes a system of categories “natural.”* ...” (Khalidi, 1998)

# HPC Kinds? Shifts the burden...

- “one can be led to lump or split the same putative kind in different ways depending on which mechanism one consults in accommodating the taxonomy to the mechanistic structure of the world” (Craver, 2009, 583).
- But... “human perspectives and conventions enter into judgments about how mechanisms should be typed and individuated” (591),
- It follows that what natural kinds there are on the HPC view will depend on those perspectives and conventions... what many will regard as an unacceptably conventionalist pluralism about what kinds of cancer kinds there are.