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Precision Medicine and Natural Kinds: Evolutionary Struggle. Disease is a Natural Kind

*Donald E Stanley**

Miane Medical Center, USA

Abstract

Disease is a natural kind, it evolves, transmutes: providing precision medicine treatment is not feasible because medical evidence is based on general tenets applicable to all patients with a disease. Diseases are not stable entities but evolve under treatment to resist treatments e.g. MRSA, Influenza, cancers, TBC. Our taxonomy of disease is based on observations that, given signs and symptoms, diseases reflect the relationship between the disease and the patient; each patient manifests symptoms and signs that mimic, but do not match exactly those in others with the same disease.

Keywords: Natural Kinds; Precision medicine; Sortals

Abbreviations

ALL: Acute lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; CLL: Chronic Lymphocytic Leukemia; MRSA: Multiple resistant Staphyloccocus aureas; TBC: Tuberculosis

Disease is a Natural Kind

A homeostatic cluster of features distinguish that it from related diseases. "We carve nature at its joints." accordingly. This notion of natural kinds is one among many diseases. Leukemia requires a predicate, a sortal predicate if you will, thus ALL, AML, CLL are categories of the disease, and yet antigenic markers (sortal predicates) distinguish among these diseases allowing targeted therapy, e.g. cytogenetics and molecular markers KIT, FLT3-ITD, NPM1, CEBPA. As our nominative classification of these diseases is based on testing for the antigen expressions, and as therapy induces changes in the cellular expressions, so the tumor cells become resistant to further elimination by transmutations to resistance; clones in Minimal Residual Disease (MRD). Discrete classes, carved at their joints, provide more specific treatments. Or so it is hoped [1,2].

Precision Medicine

Precision medicine is designed to understand and treat the nature of disease, and disease is a natural kind; in precision medicine individually. Individuals who suffer a disease should be treated as individuals, stricken with an individual disease, not as a group of sufferers with a similar disease. So, disease is different from sufferer to sufferer.

Thus, generalizability (induction) is forfeited to particularity, sensitivity to specificity, and randomized controlled trials would suffer from lack of participation since each disease would be treated somewhat differently, depending on the definition. Treatment protocols would be suited to the genomic markers of the disease and these degrees of difference might require different therapies [3,4]. This would eventually and controversially obviate the need for randomized trials.

Research Options

In place of RCTS clinical trials might include n of 1, or even master protocols such as umbrella and basket trials. One SNP does not make an entirely new disease. That is the foundation of umbrella protocols, Tumor cells regulate antigenic self-expression in order to survive the treatment by protocol drugs, and they usually succeed. Even ALL is not vanquished, thus CAR-T Therapy. Yet which tumor cells to search which CTCs or ct-DNA, to sort and harvest and insert a chimeric antigen?

Disease Persists or Recurs

Why does relapse, or failure, occur in the treatment of AML et al., [5] if the residual tumor cells are antigenically similar progeny of the originals? Simply the effect of mutagenic chemotherapy?

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Correspondence:
Donald E Stanley, Pathologist, Miane Medical Center, 22 Bramhall St, Portland, ME 04101, USA, E-mail: stanld@mmc.org

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Or subclones of the blast or progenitor population? Or do the blasts evolve and develop subsequent resistance to any and all therapeutic agents? AML is the best suited model for laboratory investigation as the disease mimics the accepted cancer stem cell model.

Controversially the definition of Cancer Stem Cells (CSC) is not yet settled: is the CSC an initiating cell, a propagating cell, or a stem-like cell [6].

Evolutionary changes in the body, dependent on both the external and internal environment (chemo and immune-therapy), allow diseases to escape natural controls i.e. the immune system and provide shields to further treatment. Sequencing of paired initial and relapse AML cells reveal relapse is reflected in minor genetic subclones initially present which survive chemotherapy. What are these cells?

Similarly, in lymphoma, tumor cells evolve to become refractory to chemotherapy, loss of responsiveness to treatment with Monoclonal Antibodies (mAbs) such as rituximab and that is a serious complication during therapy of B-cell malignancies but the mechanisms responsible for it are not well understood [7-10].

This is what one would expect from natural kinds such as ourselves; we evolve to survive ambient cultures e.g. obesity and Type II diabetes may be considered evolutionary alterations. A shift from simpler diets and activities.

The most important advance provided for precision medicine initiative will be a more specific way to define and thus to understand disease, but it will not finally be therapeutically effective since natural kinds will not easily succumb to alteration of the therapeutic milieu i.e. the treatment that will try to change this interior state. Natural kinds will adapt to interventions as quickly as they can.

As precision medicine is aimed at understanding disease, we must be able to take advantage of survival distributions; if every disease is unique, there is no purchase for induction, or path to generalize treatment. If each case of lung cancer will require different immunomodulating drugs, and the cost for one year exceeds $150,000 how shall equitable distribution be established in the non-insured population.

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