THE LANDSCAPE OF RARE CANCER: A SEA OF OPPORTUNITY

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ABSTRACT

Rare cancers, as a collective, account for approximately one-quarter of all cancer diagnoses and deaths. Historically, they have been divided into two groups. The first was defined by their unusual histogenesis (cell of origin or differentiation state), and include chordomas or adult granulosa cell tumours (aGCT). Most tumour types from this first group are still clinically and biologically relevant and have been disproportionally important as sources of insight into cancer biology. The second grouping of rare cancers were histologically defined subtypes of common cancers, most of which have been shown to have neither defining molecular features, nor clinical utility. 'Omics based analyses has splintered common cancers into a myriad of molecularly rather than histologically, defined subsets of common cancers, many of which have immediate clinical relevance. Today, almost all rare cancers are either histomolecular entities, which often have pathognomonic mutations, or molecularly defined subsets of more common cancers. The presence of specific genetic variants provides rationale for testing targeted agents in rare cancers, however, the essential contributions of both mutation and cell context in the development, biology, and behaviour of these cancers

suggest that designing trials of drugs based on the presence of mutations, without consideration of cellular context (the specific genomic and signalling architecture in which mutations operate) is naïve. Patients with rare cancers are disadvantaged due to challenges of participating in clinical trials however, the number of patients with rare cancers will only increase as more molecular subsets of common cancers are identified, and as this happens, it will be necessary to shift the focus of clinical trials and research to cancer types, which by epidemiological definitions are rare tumours.

WHAT ARE 'RARE CANCERS'?

In medicine, the designation rare is assigned based on the prevalence of disease. However, there is no agreed upon standard threshold: the World Health Organization defines rare diseases as affecting between 0.65-1 in 1000 people; the United States (US) Rare Disease Act defines rare diseases as affecting approximately one in 1500 people; the European Union officially defines rare diseases as having a prevalence of less than one in 2000 individuals; and in Japan, rare diseases are defined as affecting approximately one in 2,500 people[1-3].

Prevalence, a measure of the number of cases within a population at a specific time, is based both on incidence and survival. As an indicator of rarity, it may be misleading when it is used for chronic conditions that occur infrequently, or conversely, when it is used to describe commonly occurring diseases with poor survival. This has particular importance when describing rarity of cancers and therefore tumours are typically defined as rare based on incidence, but without a universally accepted threshold. The European Society of Medical Oncology defines rare tumours as those with an incidence lower than six per 100,000 people per year.[4, 5] By contrast, the National Cancer Institute in the US defines rare cancers as having an incidence of fewer than 15 per 100,000 people per year.[5, 6] Interestingly, by the National Cancer Institute criterion, only 11 cancer types are considered common in American adults: prostate, breast, lung, colon, uterus (endometrial), bladder, melanoma, rectum, ovary, non-Hodgkin lymphoma, and kidney/renal pelvis neoplasms (see Table 1).[7] Many of these are being sub-classified into clinically relevant, molecularly defined subgroups, as described below, and as a consequence may be losing their common cancer designation.

Although most basic research and clinical trials, at least in adults, have historically focused on common cancers, a disproportionately large amount of our understanding of cancer biology comes from the study of rare cancers. Perhaps the earliest example is the landmark epidemiological discovery from Sir Pervical Pott's study of scrotal cancers in chimney sweeps, which revealed the carcinogenic effects of tar.[8] Later, the study of retinoblastoma, which has an incidence between 0.35-1.25 per 100,000, led to the discovery of the *RB1* gene. This was the first hereditary cancer gene and the first tumour suppressor gene to be cloned,[9] and was shown to have a role in cell cycle control in cancer. Knudsen's eponymous two-hit hypothesis emerged out of the mathematical modeling of data from inherited and sporadic cases of retinoblastoma.[10] More recently, the discovery of recurrent mutations in *DICER1* in nonepithelial ovarian tumours revealed how abnormal microRNA processing can be oncogenic.[11, 12] In addition to their biologic relevance, rare cancers, collectively, are a significant source of cancer-associated mortality and, for this reason alone, merit investigation. Though

individually uncommon, rare cancers are believed to be the fourth leading cause of death each year in the United States[6] and account for 22-27% of cancer diagnoses and 25% of cancer mortality[4, 7, 13]. These numbers can only be expected to rise as genomic-based classification becomes more prevalent, resulting in the increased identification of rarer, molecularly defined subgroups of cancer.

THE NATURE OF RARE CANCERS

The classification of cancer has been based primarily on three properties: (i) where the cancer is in the body or which organ is affected, (ii) the cell type based on microscopic examination, and (iii) which mutations or other genomic aberrations drive and characterize the cancer. Before the introduction of light microscopic examination more than a century ago, cancers were classified based on their anatomical location (e.g. lung cancer). Later, microscopy allowed consideration of cell type (e.g. adenocarcinoma of lung). Finally, molecular biology and genomics revealed mutations which segregate cancers into specific treatment groups (e.g. adenocarcinoma of lung with an *ALK* translocation). The changing classification of lung cancers from histological to molecular is depicted in Figure 1. [14]

The Evolution of the Cancer Landscape through the Pre-Molecular, Molecular, and Post-Genomics Eras

Pre-Molecular Era

In the pre-molecular era, the appearance of cells by light microscopy was the primary tool used to categorize cancers, with cell lineage inferred based on where, anatomically, tumours were observed and an understanding of the histology of the relevant organ systems. **During this time, rare cancers were either tumours presumed to originate from or resembling a cell type that infrequently gave rise to cancer, or histologically defined subsets within a more common type of cancer.** The first category, tumours of unusual and recognizable histogenesis, fits more intuitively with the concept of rarity and encompasses a broad spectrum of cancers, which have, until recently, been relatively poorly characterized. The second category of rare cancers is a mixed group, variably recognizable on routine pathological examination, often associated with significant inter-observer variability in diagnosis, and with clinical impact varying from negligible to profound. For example, the classification of lung carcinomas into small cell and non-small cell histologies was critical for determination of prognosis and treatment, however the myriad number of sub-histologies within the non-small cell group did not alter their management. Without the aid of molecular correlates, it was uncertain for many tumours in this second category, whether they were meaningful and distinct clinical entities.

Molecular Era

The introduction of molecular techniques, such as immunostaining, cytogenetics, and targeted sequencing, led to the discovery of tumour-specific molecular features. What emerged from the use of these methods were two broad categories of rare tumours that still apply today. **The first are (A) rare cancers that have both a distinguishing histology and characteristic molecular changes, which we will call *histomolecular entities*. The second are (B) rare cancers that have defining molecular alterations but lack distinguishing histological characteristics. These tumours have a clinically relevant but infrequent genetic alteration within a more common type of cancer.** Genetic (and later, genomic) interrogation of cancers has led to the discovery of pathognomonic, or defining, mutations in many of the cancers defined in the pre-molecular era by unusual histogenesis. In addition, this same approach has identified

new, and often clinically relevant, subtypes of common cancers. By contrast, a number of rare tumours that once represented a distinct histological subset of a more common cancer have disappeared as a distinct diagnostic entities and instead are considered to be morphological variants that lack distinct molecular correlates within a common cancer type.

Genomics and Post-Genomics Eras

Moving from the molecular era to the genomics era drastically altered the ease of interrogating the genome to find mutations and the speed at which these mutations were identified. In the genomics era, massively parallel sequencing was ubiquitously applied to decode cancers. Groups such as The Cancer Genome Atlas and the International Cancer Genome Consortium have generated whole genome, whole transcriptome, and DNA methylation data, which have been integrated with copy number and protein expression profiles to stratify cancers.[15-17] This type of classification can be useful in understanding how different subtypes progress and respond to treatment. Taken to its extreme, however, this method of categorization renders every tumour as a unique entity. Although this will be the basis of true personalized medicine, we are not to the point where every cancer can be treated as a singular clinical management challenge, outside of the research domain. In the near term, it will be necessary to base treatment decisions on subgroupings of closely related tumours defined by consideration of cell context and genomic aberrations, prognosis, and response to treatment.

When genomic analysis first identified specific mutations across a diverse range of cancer histologies, the research community proposed that genomic rather than histologic features would be the key determinants of cancer biology, prognosis, and patient benefit from targeted treatment. Further laboratory and clinical research have clearly shown that the effects of specific mutations are dependent on cellular context, so that patient management decisions based solely on the presence of targetable mutations can be misleading. Cell type remains important in cancer classification into the post-genomic era, particularly when attempting to identify patient subgroups that may benefit from targeted treatments. We suggest that both **(A) histomolecular entities and (B) molecular subtypes of common cancers** will have enduring relevance and that these are the cancers in which targeted therapies could logically be applied (figure 2).

The Discovery of Molecular Features Changes Tumour Classification

Cancers from rare origins

The first category of rare cancers, those with unique histogenesis, has largely carried forward from the pre-molecular era (Table 2). The vast majority of these rare cancers harbour characteristic mutations and are recognized as distinct histomolecular entities. The identification of characteristic mutations has improved diagnosis of these tumours and provided more accurate indicators of their true incidence. Included in this group are gastrointestinal stromal tumours (GISTs), almost all of which have activating mutations in either *CKIT* (90% of GISTs), *PDGFRA* or other related mutations;[18-20] hairy cell leukemia (HCL), which almost always have a *BRAF* hotspot mutation (V600E);[21] and small cell carcinoma of the ovary hypercalcemic type (SCOOHT), characterised by mutations in the *SMARCA4* gene.[22-24] The incidences associated with these rare histomolecular entities are 15-20 new cases of GISTs per 10,000,000 people each year and 1 HCL case per 300,000 people each year.[25, 26] The true incidence of SCOOHT is unknown as so few cases have been reported.

Another example of this class of cancer is adult granulosa cell tumours (aGCTs) of the ovary. aGCTs were first described over 150 years ago by Rokitansky.[27] They originate

from granulosa cells, occur at a frequency of 1 in 100,000 and account for less than 5% of ovarian cancers.[28] Diagnostic accuracy based only on histopathology is limited as GCTs can resemble other neoplasms.[29] Our group used whole transcriptome sequencing of four aGCTs to identify a pathognomonic mutation in the *FOXL2* gene that results in a one amino acid change (C134W) in the transcription factor gene product.[30] We have since shown that the *FOXL2* mutation has implications for the diagnosis and classification of aGCTs and may provide clues to the pathogenesis of this tumour.[31-33] Our experience with aGCTs illustrates the principle, which has repeatedly borne out,[12, 23, 34] that the study of a small number of tumours can reveal characteristic mutations, if these tumours represent a tightly constrained clinical and biological entity, particularly one of low genomic complexity.

However, not all rare cancers with unique histogenesis have characteristic molecular alterations. Chordomas were first recognized as a histologically distinct tumour in the mid-1850s by Virchow and have an incidence of 1 case per 1,000,000 people. They are diagnosed based on their location along the spine and histology, aided by specific immunomarkers such as brachyury,[35] and are thought to emerge from persistent notochordal remnants.[36] This fits well with the embryonic rest hypothesis of cancer development, which posits that cancers develop from embryonal tissues that are produced in excess and remain in the body throughout adulthood.[37] Despite efforts by several research groups including our own, genomics technologies have failed to reveal pathognomonic changes in chordomas.[38, 39] This may be because these tumours occur as a result of many different mutations, or it may be that characteristic mutations for chordomas are yet to be discovered. Regardless, this rare tumour type persists as a distinct histological entity lacking specific molecular correlates.

Finally, some cancers were placed into this category based on mistaken presumptions about their histogenesis. Askin's tumour, for example, was originally described in 1979 as a distinct histological entity.[40] However, both Ewing's sarcoma and Askin's tumour are likely derived from a primitive neuroectodermal pluripotent cell.[41, 42] In addition, these two tumour types were later found to share common immunomarker expression, a characteristic chromosomal translocation (t(11;22)(q24;q12)), and clinical behaviour.[43, 44] Ultimately, Askin's tumours are now considered part of the larger Ewing's sarcoma family of tumours, a rare distinct histomolecular entity with characteristic translocations.

Subsets of Common Cancers

In the pre-molecular era, histologically defined subsets of common cancers were classified based on site of origin and by light microscopy. Most have failed to correlate with specific mutational events, and thus have been absorbed into a more common cancer classification (Table 3). Examples include transitional cell carcinoma of the ovary (TCC), tubular carcinoma of the breast, and giant cell carcinoma of the lung. TCC, which histologically resemble Brenner tumours but without the characteristic benign component, are regarded as a variant of high-grade serous tubo-ovarian cancers based on mutation and expression profiles.[45] While comparison of high-grade serous ovarian cancers with and without *BRCA* mutations demonstrated that TCC morphology is more frequently found among tumours with *BRCA* mutations,[46] TCC-like features are not sufficiently distinctive to facilitate identification of those women who should be screened for familial *BRCA* mutations[47]. For similar reasons (i.e. lack of clinical relevance), tubular carcinoma of the breast and giant cell carcinoma of the lung, are now classified as low-grade breast cancers, or non-small cell lung cancers (NSCLCs), respectively.

Less commonly, genetic analysis has shown that some histologically defined subsets of common cancers also have characteristic molecular changes, and accordingly should be categorized as distinct histomolecular entities. Representative of this group of rare cancers are juvenile secretory breast cancer and fibrolamellar hepatocellular carcinoma. Juvenile secretory breast cancer was originally described in 1966 by McDivitt and Stewart as a childhood mammary tumour[48] and later shown to occur more commonly in adults.[49] Compared to typical infiltrating ductal carcinoma, secretory breast cancer in children has a more favourable prognosis.[49] In 2002, Tognon *et al*. showed that secretory breast cancers are characterized by expression of the *ETV6-NTRK3* fusion gene, whose expression likely drives transformation.[50] This fusion is also found in unrelated tumours including congenital fibrosarcoma, congenital mesoblastic nephroma,[51, 52] mammary analog secretory carcinoma of salivary gland, and acute myeloid leukemia.[53, 54] However, in the context of breast tumours, the *ETV6:NTRK3* fusion is specifically expressed and is diagnostic for secretory breast cancer.[55] Fibrolamellar hepatocellular carcinomas represent less than 1% of liver cancers and was described as variant of hepatocellular carcinoma in 1956[56]. Its clinical phenotype is distinct from that of hepatocellular carcinoma and recently, through analysis of whole transcriptome sequencing data, it was reported that a *DNAJB1:PRKACA* fusion resulting from a large genomic deletion was present in tumour samples from all 11 patients studied.[57]

Common Cancers and the Emergence of Molecular Subclasses

The corollary to the reabsorption of once distinct tumour types into a more common cancer classification is the identification of molecular subsets of tumours from within a common tumour histology (Table 4). This reclassification has teased out subgroups from within more common tumour types, causing a steep increase in the number of molecular subtypes of common cancers. These molecular subclasses, which may benefit from targeted management, are largely driving the current personalized medicine initiatives, though not all molecular features can be linked to an accompanying treatment. NSCLCs are a prime example of how molecular sub-classification of a common cancer has resulted in specific treatment recommendations that improve outcomes. These were historically thought to be a single disease entity because the different histologic subtypes appeared to share the same cause, clinical characteristics, and treatment outcomes and so were uniformly managed.[58, 59] Both tumour histology and genetic mutations correlated with activity of specific cytotoxic and targeted agents. For example, patients with adenocarcinomas of the lung treated with the antifolate pemetrexed have improved survival compared to patients with squamous histology. In addition, patients with NSCLCs, which harbour activating mutations in the tyrosine kinase domain of *EGFR,* have dramatic responses to the tyrosine kinase inhibitors such as gefitinib.[60, 61] In 2007, Soda et al., showed that *EML4:ALK* fusions were found in NSCLC and that this fusion was required for transformation.[62] The *EML4:ALK* fusion was subsequently shown to be present in a small fraction of NSCLCs (2-7%),[63] the vast majority of which are negative for *EGFR* mutations.[64] This discovery led to the therapeutic evaluation of ALK inhibitors, which have been associated with a dramatic 57% response rate in patients whose NSCLC harbours the *EML4:ALK* fusion.[63] Adenocarcinomas of the lung are now generally classified by their actionable mutations, rather than morphological correlates.[65]

Large-scale consortia-driven genomic analyses are resulting in increasing numbers of molecular subgroups being distinguished from common cancers.[15-17] This multiplicity of mutation-defined subgroupings is exemplified by The Cancer Genome Atlas'

comprehensive 'omics analysis of 373 endometrial tumours.[16] From this analysis emerged a molecular classification scheme that separates endometrial tumours into four groups that correlate with survival. One of these groups, the *POLE* ultramutated group, had a considerably better prognosis compared to the other three endometrial cancer groups, despite having a histologic appearance which suggests higher risk. This finding has been validated by several research teams who have since shown that *POLE* exonuclease domain mutations correlate with clinical outcomes in endometrial cancer.[66-70] It remains to be determined whether these cancers have an indolent natural history or are ultraresponders to standard therapy. *POLE* mutated endometrial cancers represent approximately 10% of all endometrial cancers, and are rapidly becoming acknowledged as a molecularly distinct subset of endometrial cancer.[71]

The Importance of Cell Context in Classification of Rare Cancers

In addition to the mere presence of characteristic tumour mutations, the cellular context of those mutations is just as important in determining behaviour of tumours. Sometimes molecular changes seem to only affect a particular cell type, as is the case in GCTs, likely because FOXL2 expression is restricted to female gonadal stromal cells. Similarly, *DICER1* mutations, which completely shift microRNA targeting so that all 5p strand targeting is eliminated while 3p targeting is maintained,[11] are not common in all cancers, but are found in cancers of children and young adults, particularly those with embryonic features, such as in nonepithelial ovarian tumours and pleuropulmonary blastomas. This is perhaps unsurprising since the 3p microRNAs tend to be dominant in primitive and embryonic cells. Finally, approximately one-third of SCOOHT patients have tumours that lack expression of both BRG1 and BRM proteins. Together BRG1 and BRM represent the two ATPases of the SWI/SNF chromatin remodelling complex, either one of which can make up the catalytic core. Curiously, SCOOHTs appear to be the only tumour that can withstand loss of both of these ATPases. Indeed, BRM has been described as a synthetic lethal target in other BRG1 deficient cancers, such as lung adenocarcinomas. [72]

Alternatively, some molecular changes are more ubiquitous and these need to be considered within the context of a larger genomic and signalling landscape. Though mutational status may be necessary, it is not sufficient to serve as a biomarker of treatment efficacy. It is critical to consider mutation status within the context of the cancer cell. Factors such as the presence of additional mutations present within the cell that may confer resistance to the targeted treatment, or clonal populations within the tumour that lack the mutation must be taken into account in rational treatment decision making.

This is particularly important as discoveries of tumour specific mutations may lead to repurposing of existing treatments, as has been done with the tyrosine kinase receptor inhibitor, imatinib. Initially used to treat *BCR:ABL* positive chronic myelogenous leukemia, this treatment was found to be effective as well in GISTs, tumours characterised by *KIT* and *PDGFRA* mutations. However, targeting the same mutation in different tumour types does not always yield the expected result. For example, there was great interest in evaluating vemurafenib, a B-raf inhibitor initially developed to treat patients with melanomas harbouring the *BRAF* V600E mutations, to treat colorectal cancer patients with this same mutation (figure 2). The Cancer Genome Atlas has shown that approximately 7% of colorectal cancers have this *BRAF* mutation, however these tumours are also hypermutated,[15] and these other mutations may alter the effectiveness of vemurafenib. In addition, colorectal cancer cells with *BRAF* mutations

appear to have escape mechanisms to maintain proliferation in the presence of B-Raf inhibition: a synthetic lethal screen of vemurafenib resistant, *BRAF* mutation positive colorectal cancer cells demonstrated that inhibition resulted in rapid feedback activation of EGFR.[73] In the context of colorectal cancer, B-Raf inhibition may be more successful when combined with EGFR suppression,[74] or inhibition of other pathways including the PI3K/AKT or MEK pathways.[75]

Challenges to developing therapies for patients with rare cancers

Advances in cancer biology and genomic technology have led not only to the creation of multiple molecularly defined rare cancers, but are reshaping the focus and conduct of drug development. Molecular alterations identified in rare cancers not only highlight potential treatment options, but also can facilitate diagnosis. However, a challenge that emerges from molecular-based diagnostics is that diagnostic entities are evolving rapidly, making consistent case identification over time problematic, and confounding attempts at systematic data collection over time. Molecular sub-classification may be further extended to include host factors such as expression of immune markers and cell infiltrates, which are of great current interst due to the emergence of therapies specifically targeting host-tumour anergy.

Though a full discussion of immunotherapy in oncology is beyond the scope of this review, it is important to mention that it represents a rich avenue of cancer drug development. Current efforts are largely directed at agents that block negative regulators of T-cell immunity, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor-1 (PD-1). Promising results with this type of therapy have been observed in patients with renal cell cancers, NSCLCs, and melanoma[76-79], however the ability to predict response is elusive. The T-cell compartment recognizes epitopes displayed on major histocompatibility complexes (MHCs) expressed on the tumour cell surface. Tumour-specific DNA alterations that give rise to novel protein sequences can produce antigens, known as neoantigens, that are not found in the normal genome. However, not all mutations result in the production of neoantigens. It is logical and there is evidence that suggests a higher number of mutations or mutational load is associated with neoantigen production.[80, 81] Many rare cancers, such as aGCTs and SCOOHTs, have low mutational loads and appear to elicit minimal host immune responses. However, mutational load alone cannot predict response, and there have been efforts directed at trying to determine if specific mutations are associated with neoantigen production and immune response. Primary mediastinal lymphomas harbour mutations that result in CIITA gene fusions, leading to overexpression of PD-1 ligand, which impacts anti-tumour immune responses.[82] Another group has shown that mutations predicted to be accessible to T-cell antigen receptors based on structure modelling were likely to be immunogenic. [83] They showed that these mutations, which likely play significant roles in tumour cell immunogenicity, were more commonly passenger rather than driver mutations,[81] while a second group has demonstrated that CD4+ neo-antigen reactivity in melanoma is associated with private mutations.[80]

In contrast to immunotherapy, it is those mutations, often pathognomonic, that drive tumourigenesis that are relevant to development of drugs that target specific molecular alterations. Currently one-third of the approximately 150 FDA-approved drugs linked to genetic markers are for oncology. The prescription of these drugs is based on biomarker information. The majority of new drugs approved for cancer by the FDA block the activity of specific proteins in key signalling pathways, with approximately one-fifth of

drugs approved in 2014 being intended for molecular subgroups of common cancers. It is clear that consideration of a single mutation does not provide sufficient information to guide targeted therapy, and that the context of the mutation must be considered. For this reason, trials testing new agents in patients are designed to evaluate effects within histologically and molecularly defined subgroups.

There are compelling reasons for trials to test treatments for rare tumours related to unmet medical need, along with the potential that rare tumours may have disease defining oncogenic driver mutations that may be effectively targeted with dramatic therapeutic effect. However, there are specific challenges to mounting trials, most obviously the low incidence of rare cancers. Cancer centres may be disinclined to participate in rare tumour trials due to the resources required to initiate and maintain a trial with limited accrual. International collaborations to increase access to trials for patients and accelerate trial accrual add considerable costs and complexity. To increase the capability to conduct trials of novel therapies for patients with rare cancer will require an investment and alignment of preclinical and clinical researchers, industry, regulatory agencies, and health care payors.

The International Rare Cancer Initiative (IRCI) aims to address the challenges of conducting intervention trials in rare cancer setting[13, 84]. IRCI is joint initiative of the Cancer Research UK (CRUK), the National Institute of Health Research Clinical Research Network: Cancer (NIHR CRN:Cancer), the National Cancer Institute (NCI), the European Organisation for Research and Treatment of Cancer (EORTC), the Institut National Du Cancer (INCa) and the NCIC Clinical Trials Group (NCIC CTG). IRCI facilitates the development of international clinical trials for patients with rare cancers by promoting meetings of researchers to develop priority questions, address design issues and facilitate execution. IRCI and other groups have promoted novel designs including multi-cohort and adaptive designs to maximize scientific knowledge gained and efficiency of conduct. At the outset of the initiative, clinical research groups were asked to identify rare cancers where there was enthusiasm for international collaborations and the potential for development of an interventional clinical trial supported within at least two of the lead organizations. To date, ten rare cancers have been selected and have formed the core activities of IRCI. These efforts, along with development of drugs by pharmaceutical companies that target molecular alterations present in rare cancers and support from funding agencies to study rare cancers, will hopefully improve treatment options available to patients with rare tumours.

Potential treatments should be tested in cell context specific model systems before use in patients. These types of experiments do not represent a significant barrier to developing treatments and must be done before evaluating drugs across multiple cancer types that share genomic targets. To bypass acquisition of this data is irresponsible medicine and perhaps hubristic. The clinical research community is responding to these challenges by forming consortia to study rare cancers and designing multiphase, multiarm adaptive “umbrella” and “basket” trials with several defined cohorts for testing targeted therapies. Such trials increase efficiency by providing opportunity to simultaneously evaluate multiple agents within multiple cohorts of patients with histologically and molecularly defined cancers. The cohorts may be modified over time depending on the activity seen with agents. Regulators and payors have indicated an openness to novel trial designs to speed assessment and time to approval, and a willingness to accept post-marketing evaluations to generate additional safety and effectiveness data.

Conclusions

In the post-genomics era, with respect to cancer taxonomy, rare is the new common. Many cancers derived from unusual histologic origins are now understood to be histomorphological entities often with pathognomonic mutations. Molecular, in particular genomic analysis, is revealing an ever-expanding number of rarer molecular subclasses of the more common cancers. This is leading to a more objective categorization of tumour types. As we move forward, it will be important to remember that for molecular sub-classification to be embraced, it must be clinically relevant.

While genomic evaluation can lead to the discovery of features that can be rapidly translated into diagnostics and monitoring tools, the development of treatment approaches for cancers where mutational events have been identified will require cell context specific models, along with development of novel targeted therapies. There is an urgent need for these types of model systems for rarer cancers, and perhaps this should be a focus for future research. Although molecular discoveries have intrinsic value for patients with these rare cancers, they may also lead to more generic strategies to better manage the ever-increasing number of clinically relevant molecularly defined subgroups of common cancers. The importance of cell context in determining the oncogenicity and targetability of mutations in rare cancers is a salient reminder that the naïve targeting of molecular features in common cancers and across cancer types, without consideration of cell context is likely to produce discouraging results.

While clinical trials in rarer cancers have historically been difficult due to low numbers of cases, trials are now being facilitated due to improved identification of these rarer entities, flexibility and innovation in design of trials that may test multiple drugs in multiple defined patient populations over time. Ideally, regulatory authorities working in concert to develop common approaches to review of trials and marketing applications for rare cancers that recognize the challenges of conducting trials in rare cancer settings and providing means to capture outcomes of patients post approval should lead to better treatment options for patients with rare cancer.

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Preferred Degrees:
NB has a PhD
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Figure Legends

Figure 1: Classification of lung adenocarcinomas without consideration of molecular features (top) from RARECARE (from 70 population-based cancer registries between1995-2002). The bottom chart represents the prevalence of molecular features in adenocarcinomas (n=733), from The Lung Cancer Mutation Consortium[14]. ROS1 or RET fusions are each present in 1% of lung carcinomas and have been added to this chart, though not assessed in this cohort.

Figure 2: The changing classification of cancers. The box size correlates approximately with the proportions of each of these categories of cancer types and the width of the arrows approximates their proportional reclassification in the post-genomics era. A representative example for each classification shift is shown (200X magnification, scale bars=100 μm). Molecular features identified with these tumour types are indicated in brackets. Tubular carcinoma of the breast, once considered its own tumour type, is now classified as low-grade ductal carcinoma of breast.

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Figure 1

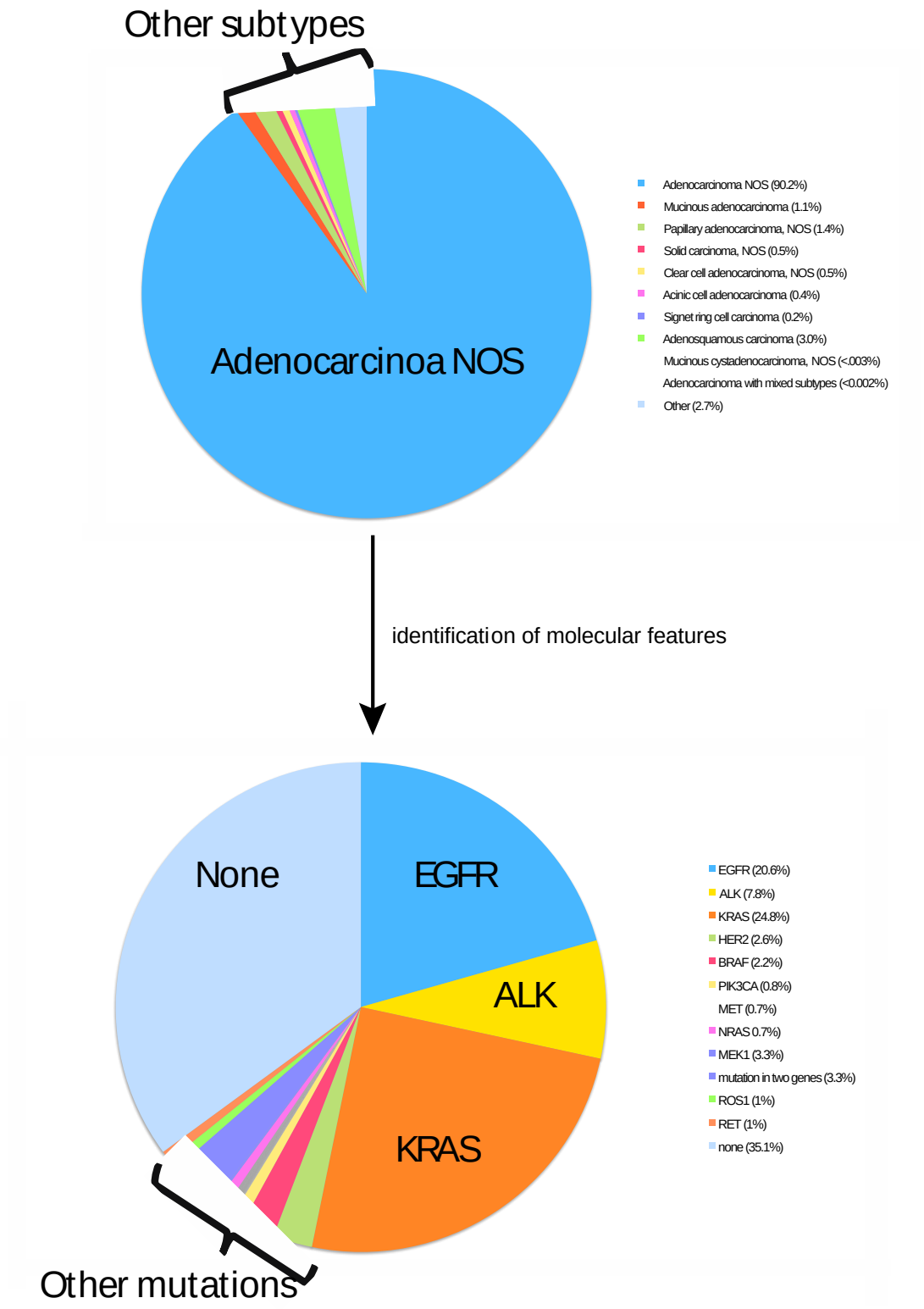
Other subtypes
Adenocarcinoa NOS
Adenocarcinoma NOS (90.2%)
Mucinous adenocarcinoma (1.1%)
Papillary adenocarcinoma, NOS (1.4%)
Solid carcinoma, NOS (0.5%)
Clear cell adenocarcinoma, NOS (0.5%)
Acinic cell adenocarcinoma (0.4%)
Signet ring cell carcinoma (0.2%)
Adenosquamous carcinoma (3.0%)
Mucinous cystadenocarcinoma, NOS (<.003%)
Adenocarcinoma with mixed subtypes (<0.002%)
Other (2.7%)
identification of molecular features
None
EGFR
ALK
KRAS
Other mutations
EGFR (20.6%)
ALK (7.8%)
KRAS (24.8%)
HER2 (2.6%)
BRAF (2.2%)
PIK3CA (0.8%)
MET (0.7%)
NRAS 0.7%)
MEK1 (3.3%)
mutation in two genes (3.3%)
ROS1 (1%)
RET (1%)
none (35.1%)

Figure 2

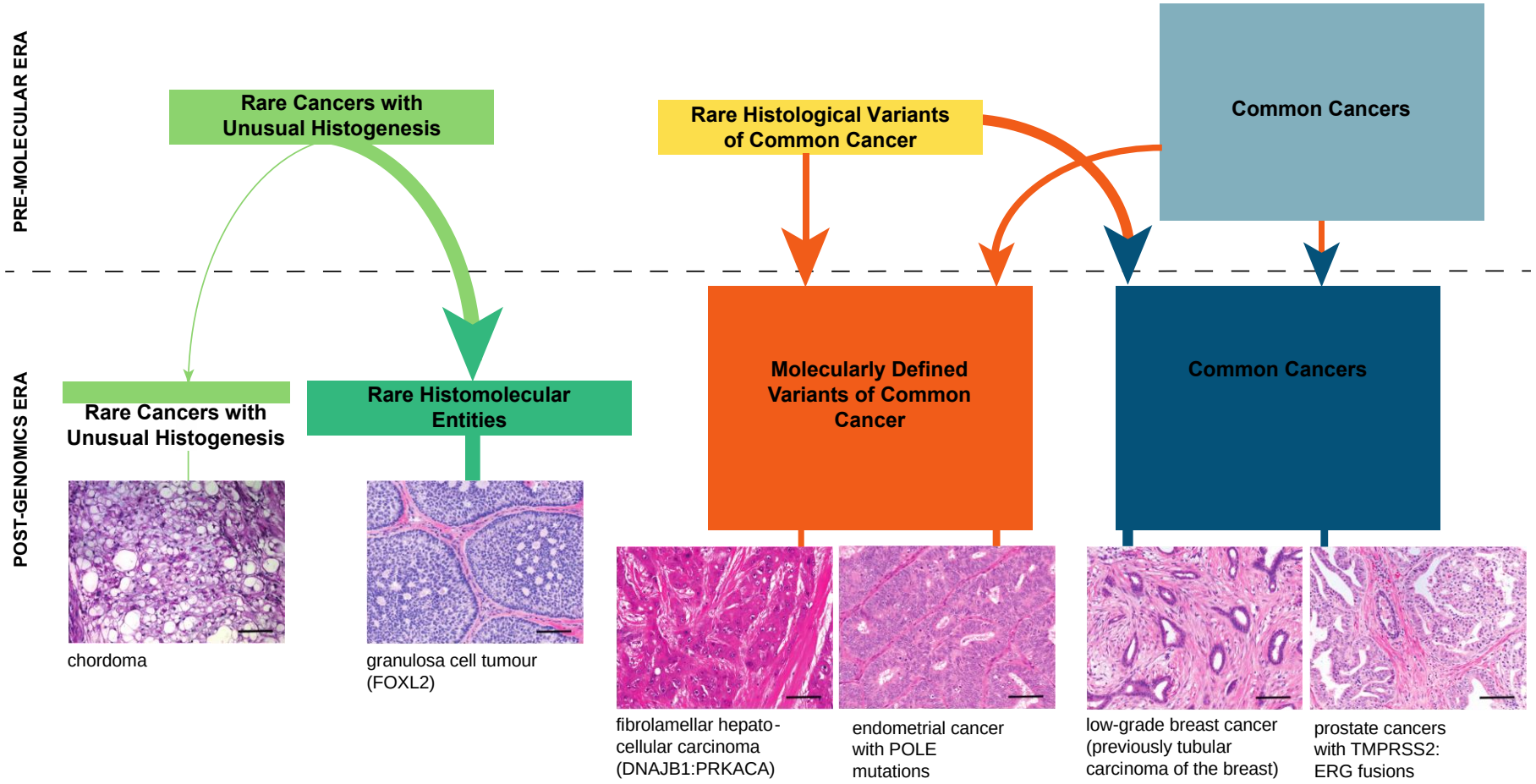
PRE-MOLECULAR ERA
POST-GENOMICS ERA
Rare Cancers with Unusual Histogenesis
Rare Histological Variants of Common Cancer
Common Cancers
Rare Cancers with Unusual Histogenesis
Rare Histomolecular Entities
Molecularly Defined Variants of Common Cancer
Common Cancers
chordoma
granulosa cell tumour (FOXL2)
fibrolamellar hepato-cellular carcinoma (DNAJB1:PRKACA)
endometrial cancer with POLE mutations
low-grade breast cancer (previously tubular carcinoma of the breast)
prostate cancers with TMPRSS2: ERG fusions

Table 1: Incidences of Selected Common and Rare Cancers

Tumours	RARECARE	CINA (1)
	Incidence (per 100,000)	Incidence (per 100,000)
Common Cancers		
prostate	47.89	215.65
breast[a]	63.85	96.18
lung[a]	55.93	85.49
colon[a]	42.64	53.49
uterus[a]	10.40[b]	32.06[b]
bladder	20.11	29.95
rectum[a]	17.11	20.30
ovary[a]	9.39[b]	17.99[b]
kidney[a]	10.55[c]	15.81[c]
melanoma	48.58	21.26
Non-Hodgkin lymphoma[a]	17.45	17.36
stomach[a]	15.23[d]	10.43[d]
IRCI Selected Rare Cancers[e]		
fibrolamellar hepatocellular carcinoma	0.01	NR
gynaecological sarcoma	0.50	NR
thymoma	0.13	NR
metastatic anal cancer	1.09	1.92
penile cancer	0.62	0.12
small bowel adenocarcinoma	0.72	2.31
salivary gland cancer	0.73	1.61
ocular melanoma	0.65	NR
anaplastic thyroid cancer	0.17	NR
rare brain cancer	0.78[f]	NR

Incidences for both common and rare cancers are based on data reported by the Surveillance of Rare Cancers in Europe (RARECARE, left hand column) and the Cancer in North America (CINA) dataset (right hand column). RARECARE figures are derived from reports from 70 European population based cancer registries adhering to the RARECARE project during the period 1995-2002. The CINA database covers 80% of the U.S. population (1995-2004 dataset from 41 population-based cancer registries). The common cancers selected are those cited by Greenlee[7] to be common based on the definition of rare cancers from the National Cancer Institute in the U.S. (those with incidences greater than 15 per 100,000) year[5,6]. The ten rare cancers shown are those the International Rare Cancer Initiative (IRCI) has chosen to focus on for development of clinical trials. The total incidence of rare cancers, estimated to be between 22-25% of all cancer diagnoses is reported in the table footnotes[4,13].

NR: not reported

(a) though considered common, portions of these cancers have molecular features that merit their classification as rare molecularly defined variants of common cancer

(b) these cancers only affect women, however RARECARE dataset reports incidence in entire population while CINA dataset[7] reports sex-specific incidence

(c) common based on CINA dataset[7], however, RARECARE incidence is lower than 15 per 100,000

(d) not common based on CINA dataset[7], however, RARECARE incidence is greater than 15 per 100,000

(e) the combined incidence of all rare cancers is estimated to be 22-27%[4,13] of all cancers which equates to an incidence of 66.02 - 81.03 per 100,000

(f) combined incidence based on all cases reported b RARECARE of oligodendroglial tumours of the central nervous system (CNS), ependymal tumours of CNS, and non-glial tumours of CNS and pineal gland

Table 2: Today's View of Cancers Previously Categorized as Rare with Unusual Histogeneis: Illustrative Examples

Pre-Molecular Classification of 'Rare Cancer With Unusual Histogenesis'	**Pathognomonic Mutation**	**Post-Genomics Classification**
GIST	*KIT* or *PDGFRA*	Rare Histomolecular Entity
HCL	*BRAF (V600E)*	Rare Histomolecular Entity
GCT	*FOXL2 (C134W)*	Rare Histomolecular Entity
SCOOHT	*SMARCA4*	Rare Histomolecular Entity
Rb	*RB1*	Rare Histomolecular Entity
Askin's Tumour	t (11,22)(q24,q12)	Rare Histomolecular Entity – part of larger ESFT
Peripheral neuroepithlioma	t (11,22)(q24,q12)	Rare Histomolecular Entity – part of larger ESFT
Esthesioneuroblastoma	t (11,22)(q24,q12)	Rare Histomolecular Entity – part of larger ESFT
Ewing's Sarcoma	t (11,22)(q24,q12)	Rare Histomolecular Entity – part of larger ESFT
Chordoma	none	Rare Cancer of Unusual Histogenesis*
Reticulum Cell Sarcoma	none	Common Cancer (B-cell lymphoma)

* *Though pathognomonic mutations have been identified for chordomas, this tumour type persists as distinct diagnostic entitiy. Because no specific molecular features are at attributed to this tumour type, it cannot be classified as a histomolecular entity, but rather retains its same pre-molecular classification of rare cancer with unusual histogenesis.*

Abbreviations
GIST: Gastrointestinal stromal tumours
HCL: Hairy cell leukemia
GCT: Granulosa Cell Tumours
SCOOHT: Small Cell Tumours of the Ovary Hypercalcemic Type
Rb: Retinoblastoma
ESFT: Ewing's Sarcoma Family of Tumours

Table 3: Today's View of Cancers Previously Categorized as Rare Histological Variants of Common Cancers: Illustrative Examples

Pre-Molecular Classification of 'Rare Histological Variant of Common Cancer'	**Pathognomonic Mutation**	**Post-Genomics Classification**
Juvenile Secretory Breast Cancer	*ETV6:NTRK3* fusion	Molecularly Defined Variants of Common Cancer
Polymorphous low-grade adenocarcinoma	*PRKD1 (E710D)*	Molecularly Defined Variants of Common Cancer
High-grade endometrial stromal sarcoma	*YWHAE:FAM22* fusion	Molecularly Defined Variants of Common Cancer
Fibrolamellar hepatocellular carcinoma	*DNAJB1-PRKACA* fusion	Molecularly Defined Variants of Common Cancer
Tubular carcinoma of the breast*	none	Common Cancer (low-grade breast cancer)
TCC*	none	Common Cancer (high-grade carcinoma of the ovary)

** These are two examples of cancers defined in the pre-molecular era as 'rare histological variants of common cancers' that are now included to be part of a larger common cancer type. The common cancer types that they are considered part of are indicated in brackets.*

Abbreviations
TCC: Transitional cell carcinoma of the ovary

Table 4: Today's View of Cancers Previously Categorized as Common Cancers: Illustrative Examples

Pre-Molecular Classification of 'Common Cancer'	**Pathognomonic Mutation**	**Post-Genomics Classification**
endometrial cancer	*POLE*	Molecularly defined subtype of common cancer
breast cancer	*HER2* amplification	Molecularly defined subtype of common cancer
high-grade serous ovarian cancer	*BRCA*	Molecularly defined subtype of common cancer
NSCLC	*EML4:ALK* fusion	Molecularly defined subtype of common cancer
prostate cancer	*TMPRSS2:ERG* fusion	Common Cancer (prostate cancer)*
High-grade serous ovarian cancer	*TP53*	Common Cancer (high-grade serous ovarian cancer)*

* *Though a fraction of prostate cancers and high-grade serous-ovarian cancers have either* TMPRSS2:ERG *or* TP53 *mutations associated with them, respectively, this has not resulted in reclassification of these tumours as 'molecularly defined subtypes of common cancer'. The rationale for this is that there are no observable differences between tumours with the specified molecular changes and tumours without, beyond the presence of the mutation itself, with respect to clinical course, treatment options, etc.*

Abbreviations
NSCLC: Non-small cell lung cancers