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Rare cancers: a sea of opportunity

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Rare cancers, as a collective, account for around a quarter of all cancer diagnoses and deaths. Historically, they have been divided into two groups: cancers defined by their unusual histogenesis (cell of origin or differentiation state)—including chordomas or adult granulosa cell tumours—and histologically defined subtypes of common cancers. Most tumour types in the first group are still clinically and biologically relevant, and have been disproportionately important as sources of insight into cancer biology. By contrast, most of those in the second group have been shown to have neither defining molecular features nor clinical utility. Omics-based analyses have splintered common cancers into a myriad of molecularly, rather than histologically, defined subsets of common cancers, many of which have immediate clinical relevance. Now, 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 the testing of targeted drugs in rare cancers. However, in addition to molecular alterations, it is crucial to consider the contributions of both mutation and cell context in the development, biology, and behaviour of these cancers. Patients with rare cancers are disadvantaged because of the challenge of leading clinical trials in this setting due to poor accrual. However, the number of patients with rare cancers will only increase as more molecular subsets of common cancers are identified, necessitating a shift in the focus of clinical trials and research into these cancer types, which, by epidemiological definitions, will become rare tumours.

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This is the first in a **Series** of three papers about rare cancers

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Introduction

In medicine, the designation "rare" is assigned on the basis of disease prevalence. However, no standard threshold is agreed upon.[1–3] WHO defines rare diseases as those affecting 0·65–1 people per 1000.[1] According to the US Rare Diseases Act, rare diseases affect roughly one in every 1500 people.[2] The European Union officially defines rare diseases as diseases with a prevalence of less than one in 2000 individuals, whereas in Japan, rare diseases by definition affect around one in every 2500 people.[3]

Prevalence is a measure of the number of cases within a population at a specific time and is determined by two factors: incidence and survival. It can be a misleading indicator of rarity, because it cannot distinguish chronic disorders that occur infrequently from commonly occurring diseases associated with poor survival.[4] This shortcoming is of particular importance when describing the rarity of cancers, and therefore tumours are typically defined as rare on the basis of incidence (ie, the number of new cases in a given period), but without a universally accepted threshold. The European Society for Medical Oncology defines rare tumours as those with an incidence of less than six per 100 000 people per year.[4,5] According to the US National Cancer Institute, rare cancers are those with an incidence of less than 15 per 100 000 people per year.[5,6] By the National Cancer Institute definition, only 11 cancer types are classed as common in US adults: prostate, breast, lung, colon, uterus (endometrial), bladder, melanoma, rectum, ovary, non-Hodgkin lymphoma, and kidney or renal pelvis neoplasms (table 1).[7] However, many of these common cancers are being subclassified into clinically relevant, molecularly defined subgroups, and might lose their common cancer designation as a result.

Although most basic research and clinical trials, at least in adults, have historically focused on common cancers, it could be argued that a disproportionately large amount of understanding of cancer biology comes from the study of rare cancers. Perhaps the earliest example is the landmark epidemiological discovery of the carcinogenic effects of tar as a result of Sir Percival Pott's study of scrotal cancers in chimney sweeps.[8] The study of retinoblastoma, which has an incidence of 0·35–1·18 per 100 000 people per year,[9,10] led to the discovery of the *RB1* gene—one of the first hereditary cancer and tumour suppressor genes to be cloned[11]—which has a role in cell-cycle control in cancer. Alfred Knudson's eponymous two-hit hypothesis emerged from mathematical modelling of data from inherited and sporadic cases of retinoblastoma.[12] More recently, the discovery of recurrent mutations in *DICER1* in non-epithelial ovarian tumours showed how abnormal microRNA (miRNA) processing can be oncogenic.[13,14]

In addition to their biological relevance, rare cancers, collectively, are a substantial source of cancer-associated mortality and thus merit investigation. Although individually uncommon, rare cancers are thought to be the fourth leading cause of death each year in the USA,[6] and account for 22–27% of cancer diagnoses and 25% of cancer mortality.[4,7,15] These numbers will probably rise as genomic-based classification becomes more prevalent, which will result in the increased identification of rarer, molecularly defined subgroups of cancer.

Evolution of the cancer landscape

Pre-molecular era

The classification of cancer has been primarily based on three properties: the part of the body or organ affected, the cell type based on microscopic examination, and the

	RARECARE incidence (per 100 000 per year)	CINA incidence (per 100 000 per year)
Common cancers		
Prostate	47·89	215·65
Breast*	63·85	96·18
Lung*	55·93	85·49
Colon*	42·64	53·49
Uterus*	10·40	32·06
Bladder	20·11	29·95
Rectum*	17·11	20·30
Ovary*	9·39	17·99
Kidney*	10·55†	15·81†
Melanoma	48·58	21·26
Non-Hodgkin lymphoma*	17·45	17·36
Stomach*	15·23‡	10·43‡
IRCI-selected rare cancers		
Fibrolamellar hepatocellular carcinoma	0·01	..
Gynaecological sarcoma	0·50	..
Thymoma	0·13	..
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	..
Anaplastic thyroid cancer	0·17	..
Rare brain cancer§	0·78	..

Incidences for both common and rare cancers are based on data reported by the RARECARE and CINA datasets. RARECARE figures are derived from reports from 70 European population-based cancer registries, which adhered to the RARECARE project from 1995 to 2002. The CINA database covers 80% of the US population (1995–2004 dataset from 41 population-based cancer registries). The common cancers selected are those with incidences greater than 15 per 100 000 in either the RARECARE or CINA datasets.[5,6] The ten rare cancers shown are those that the IRCI has chosen to focus on for development of clinical trials. The total incidence of rare cancers is estimated to be 66·02–81·03 per 100 000 per year.[4,13] For sex-specific cancers, the RARECARE dataset reports incidence in the entire population, whereas the CINA dataset reports by sex. RARECARE=Surveillance of Rare Cancers in Europe. CINA=Cancer in North America. IRCI=International Rare Cancers Initiative. *Although deemed common, some subgroups within these cancers have molecular features that merit their classification as rare molecularly defined variants of common cancer. †Common based on CINA dataset. ‡Common based on RARECARE dataset. §Combined incidence based on all cases reported to RARECARE of oligodendroglial tumours of the CNS, ependymal tumours of the CNS, and non-glial tumours of the CNS and pineal gland.

Table 1: **Yearly incidences of selected common and rare cancers**

mutations or other genomic aberrations that drive and characterise the cancer (figure 1).[16] Before the introduction of light microscopy to pathology practice more than a century ago, cancers were classified on the basis of anatomical location (eg, lung cancer). Later, microscopy allowed for consideration of cell type (eg, adenocarcinoma of lung), with cell lineage inferred on the basis of where anatomically tumours were noted and an understanding of the histology of the relevant organ. The advent of molecular biology and genomics led to the discovery of mutations that divided cancers into specific treatment groups (eg, adenocarcinoma of lung with an *ALK* translocation).

In the pre-molecular era rare cancers were either tumours presumed to originate from or resemble a cell type that infrequently gave rise to cancer, or histologically defined subsets within a more common type of cancer (figure 2). The first category—ie, tumours of unusual and recognisable cell type—fits more intuitively with the notion of rarity and encompasses a broad range of cancers, which were poorly characterised before the introduction of molecular diagnostics. The second group are cancers that are variably recognisable during routine pathological examinations, often associated with substantial inter-observer variability in diagnosis, and associated with varying clinical effects, from negligible to profound. For example, the classification of lung carcinomas into small-cell and non-small-cell histologies was crucial for determination of prognosis and treatment. However, the myriad sub-histologies within the non-small-cell group did not affect clinical management. Without the aid of molecular correlates, whether many histologically defined subsets of common tumours were meaningful and distinct clinical entities was difficult to ascertain.

Molecular, genomic, and post-genomic era

The introduction of molecular techniques, such as immunostaining, cytogenetics, and targeted sequencing, led to the discovery of tumour-specific molecular features. Two broad categories of rare tumours resulted, which still apply: rare cancers that have both a distinguishing histology and characteristic molecular changes, which we term histomolecular entities, and rare cancers that have defining molecular alterations but no distinguishing histological characteristics (figure 2). The tumours in this second group have a clinically relevant but infrequent genetic alteration and are often subtypes of a more common type of cancer.

Genetic—and later, genomic—investigation of cancers has led to the discovery of pathognomonic (ie, defining) mutations in many of the cancers defined in the pre-molecular era by unusual histogenesis. Additionally, this approach has been used to identify new and often clinically relevant subtypes of common cancers. By contrast, several rare tumours that once represented a distinct histological subset of a more common cancer are no longer thought of as distinct diagnostic entities and instead are thought to be morphological variants that lack distinct molecular correlates within a common cancer type (figure 2).

The advent of genomics substantially expedited the interrogation of the genome and the identification of mutations. 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.[17–19] 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 classification renders every tumour a unique entity. Although such a system will be the basis of truly personalised medicine, the point at which every cancer can be treated as a singular clinical entity has not yet been reached 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 cell context, genomic aberrations, prognosis, and response to treatment.

When genomic analysis was first used to identify specific mutations across a diverse range of cancer histologies, the research community proposed that genomic rather than histological features would be the key determinants of cancer biology, prognosis, and benefit from targeted treatment. Further laboratory and clinical research has clearly shown that the effects of specific mutations are dependent on cellular context,[20] and thus management decisions based solely on the presence of targetable mutations can be misleading. Cell type remains important in cancer classification in the post-genomic era, particularly when attempting to identify subgroups of patients who might benefit from targeted treatments. We suggest that both histomolecular entities and 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).

Molecular features and tumour classification

Cancers from rare origins

The first category of rare cancers, those with unique histogenesis, has largely been carried forward from the pre-molecular era (table 2). Most of these rare cancers also harbour characteristic mutations and are recognised as distinct histomolecular entities. The identification of characteristic mutations has improved diagnosis of these tumours and provided more accurate indicators of their true incidence. This group includes gastrointestinal stromal tumours, almost all of which have activating mutations in either *c-KIT* (90%), *PDGFRA*, or other related mutations;[21–23] hairy cell leukaemia, which is almost always associated with the $BRAF^{V600E}$ mutation;[24] and small-cell carcinoma of the ovary hypercalcaemic type, characterised by mutations in the *SMARCA4* gene.[25–27] The incidence of gastrointestinal stromal tumours is 15–20 new cases per 10 000 000 people per year; that of hairy cell leukaemia is one case per 300 000 people per year.[28,29] The true incidence of small-cell carcinoma of the ovary hypercalcaemic type is unknown as so few cases have been reported.

Adult granulosa cell tumours of the ovary are another class of cancers with unique histogenesis. They were first described more than 150 years ago by Carl von Rokitansky.[30] They originate from granulosa cells, occur at a frequency of one case per 100 000 people per year, and account for less than 5% of ovarian cancers.[31] Diagnostic accuracy based on histopathology only is limited because granulosa cell tumours can resemble other neoplasms and other sex-cord tumours and epithelial malignancies to be misclassified as granulosa cell tumours.[32] We used whole-transcriptome sequencing of four adult granulosa cell tumours to identify a mutation in the *FOXL2* gene that results in a one aminoacid change (Cys134Trp) in the transcription factor gene product.[33] We have since shown that the *FOXL2* mutation has implications for the diagnosis and classification of adult granulosa cell tumours and could provide clues about the pathogenesis.[34–36] Because the *FOXL2* mutation is nearly always present in granulosa cell tumours, it can be used to prevent misclassification, which is important because true granulosa cell tumours are largely indolent, and most deaths attributed to them are probably the result of misdiagnosis of other tumours. Our experience shows

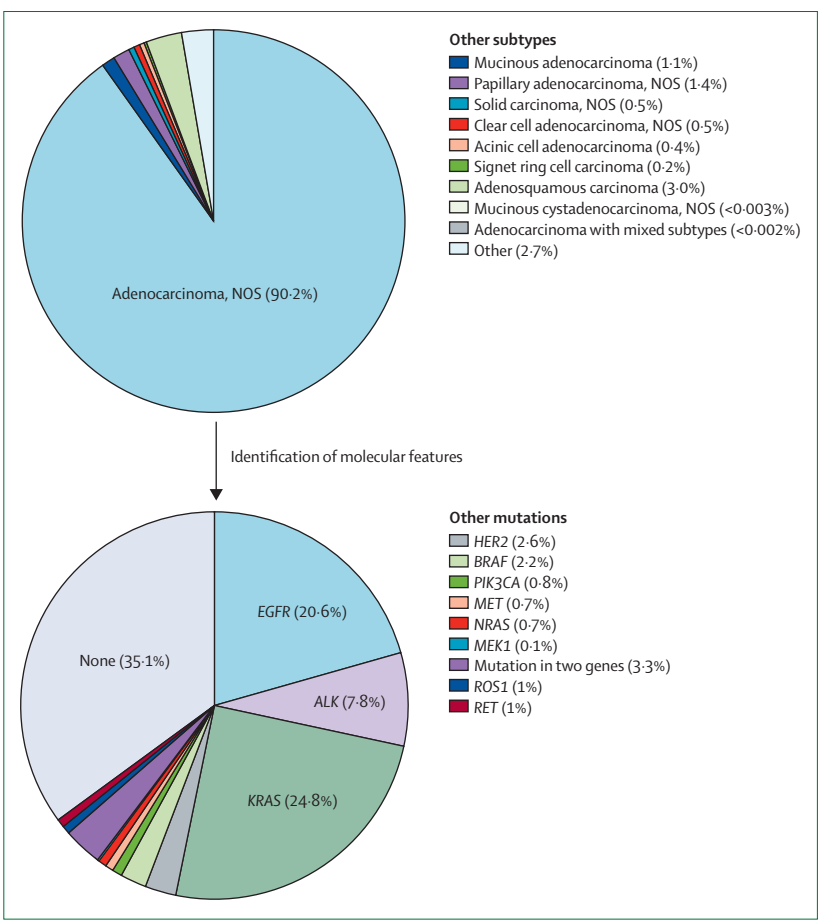

Figure 1: **Classification of lung adenocarcinomas without consideration of molecular features, and prevalence of molecular features in adenocarcinomas**

Data for the top chart are from Surveillance of Rare Cancers in Europe, and were provided by 70 population-based cancer registries between 1995 and 2002. Data for the bottom chart are from the Lung Cancer Mutation Consortium (n=733).[16] *ROS1* or *RET* fusions are each present in 1% of lung carcinomas and have been added to this chart, but they were not assessed in this cohort. NOS=not otherwise specified.

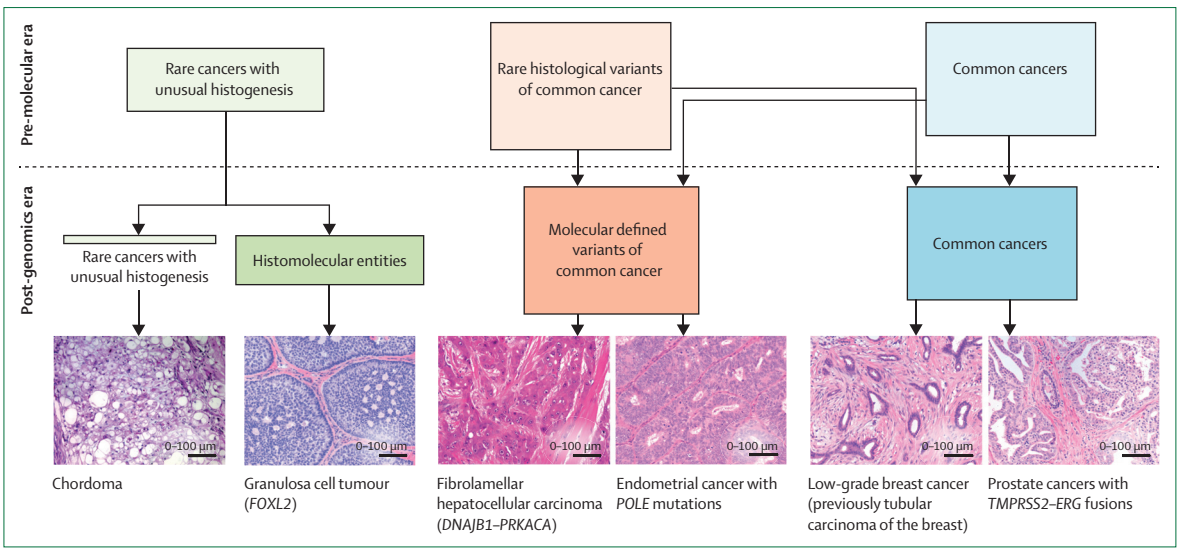

Figure 2: **Changing classification of cancers**
Box size roughly represents the proportions of each of these categories of cancer types. A representative example for each classification shift is shown (200× magnification). Molecular features identified with these tumour types are shown.

	Pathognomonic mutation	Post-genomics classification
Gastrointestinal stromal tumours	*KIT* or *PDGFRA*	Histomolecular entity
Hairy cell leukaemia	*BRAF*^{V600E}	Histomolecular entity
Granulosa cell tumours	*FOXL2* (C134W)	Histomolecular entity
Small-cell tumours of the ovary hypercalcaemic type	*SMARCA4*	Histomolecular entity
Retinoblastoma	*RB1*	Histomolecular entity
Askin's tumour	t(11;22)(q24;q12)	Histomolecular entity—part of larger Ewing's sarcoma family of tumours
Peripheral neuroepithelioma	t(11;22)(q24;q12)	Histomolecular entity—part of larger Ewing's sarcoma family of tumours
Esthesioneuroblastoma	t(11;22)(q24;q12)	Histomolecular entity—part of larger Ewing's sarcoma family of tumours
Ewing's sarcoma	t(11;22)(q24;q12)	Histomolecular entity—part of larger Ewing's sarcoma family of tumours
Chordoma	..	Rare cancer with unusual histogenesis*
Reticulum cell sarcoma	..	Common cancer (B-cell lymphoma)

*Although pathognomonic mutations have been identified for chordomas, this tumour type persists as a distinct diagnostic entity. No specific molecular features are attributed to this tumour type, which means that chordoma cannot be classified as a histomolecular entity but rather retains the pre-molecular classification of rare cancer with unusual histogenesis.

Table 2: **Post-genomics classification of cancers previously classed as rare with unusual histogenesis**

the principle, which has repeatedly borne out,[14,26,37] that the study of a few tumours can reveal characteristic mutations, if these tumours represent a tightly constrained clinical and biological entity, particularly one of low genomic complexity and heterogeneity.

However, not all rare cancers with unique histogenesis have characteristic molecular alterations. Chordomas were first recognised as a histologically distinct tumour in 1857 by Rudolf Virchow[38] and have an incidence of one case per 1 000 000 people per year. They are diagnosed on the basis of their location along the spine and histology and the presence of specific immunomarkers (such as expression of the brachyury protein).[39] Chordomas are thought to emerge from persistent notochordal remnants,[40] and this idea 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.[41] Despite efforts by several research groups, including ours, genomics technologies have not shown pathognomonic changes in chordomas[42,43]—perhaps because these tumours occur as a result of many different mutations, or because the characteristic mutations for chordomas have yet to be discovered. Therefore, this rare tumour type persists as a distinct histological entity without specific molecular correlates.

Some cancers were placed into the unique histogenesis category on the basis of mistaken presumptions. For example, Askin's tumour, a round cell tumour of the thoracopulmonary region, was originally described in 1979 as a distinct histological entity.[44] However, both Ewing's sarcoma and Askin's tumour are probably derived from a primitive neuroectodermal pluripotent cell.[45,46] Additionally, these two tumour types express common immunomarkers, share a characteristic chromosomal translocation, t(11;22)(q24;q12), and exhibit similar clinical behaviour.[47,48] Ultimately, Askin's tumours are now thought to be 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 on the basis of site of origin and by light microscopy. Most of these subsets

do not 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, tubular carcinoma of the breast, and giant cell carcinoma of the lung. Transitional cell carcinomas of the ovary, which histologically resembles Brenner tumours but are not benign, are thought to be variants of high-grade serous tubo-ovarian cancers on the basis of mutation and expression profiles.[49] Although study of high-grade serous ovarian cancers has shown that the morphology of transitional cell carcinoma is more frequent among tumours with *BRCA* mutations,[50] transitional cell carcinoma-like features are not sufficiently distinctive to enable identification of people who should be screened for familial *BRCA* mutations.[51] For similar reasons (ie, lack of clinical relevance), tubular carcinoma of the breast and giant cell carcinoma of the lung are now classified as common cancers—low-grade breast cancers or non-small-cell lung cancers (NSCLCs), respectively.

Genetic analysis has shown that some histologically defined subsets of common cancers are also associated with characteristic molecular changes, and accordingly should be classed 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[52] but was later shown to occur more commonly in adults.[53] Compared with typical infiltrating ductal carcinoma, secretory breast cancer in children has a more favourable prognosis.[53]

In 2002, Tognon and colleagues[54] showed that secretory breast cancers are characterised by expression of the *ETV6–NTRK3* fusion gene, the expression of which is thought to drive transformation.[54] This fusion is also present in unrelated tumours, including congenital fibrosarcoma, congenital mesoblastic nephroma,[55,56] mammary analogue secretory carcinoma of salivary gland, and acute myeloid leukaemia.[57,58] However, in the context of breast tumours, the *ETV6–NTRK3* fusion is specifically expressed, and is diagnostic for, secretory breast cancer.[59]

Fibrolamellar hepatocellular carcinoma represents less than 1% of liver cancers and was described as a variant of hepatocellular carcinoma in 1956.[60] Its clinical phenotype is distinct from that of hepatocellular carcinoma and, in 2014, analysis of whole transcriptome sequencing data showed that a *DNAJB1–PRKACA* fusion resulting from a large genomic deletion was present in tumour samples from all 11 patients studied.[61]

Molecular subclasses of common cancers

The corollary to the reabsorption of once-distinct tumour types into a 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 common tumour types, causing a steep increase in molecular subtypes. These molecular subclasses, which could benefit from targeted management, are largely driving personalised medicine initiatives, though not all molecular features can be linked to an accompanying treatment.

NSCLCs are a prime example of how molecular subclassification of a common cancer has resulted in specific treatment recommendations that improve outcomes. NSCLCs were historically thought to be a single disease entity because the different histological subtypes seemed to share the same risk factors, clinical characteristics, and treatment outcomes, and so were uniformly managed.[62,63] Both tumour histology and genetic mutations correlated with activity of specific cytotoxic and targeted drugs. For example, patients with adenocarcinomas of the lung given the antifolate pemetrexed had significantly improved overall survival compared with those with squamous histology (9·0 months *vs* 6·2 months).[64–66] Additionally, patients with NSCLCs that harbour activating mutations in the tyrosine-kinase domain of *EGFR* have substantial responses to tyrosine-kinase inhibitors such as gefitinib.[67,68]

	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–NUTM2A/B* fusion*	Molecularly defined variants of common cancer
Fibrolamellar hepatocellular carcinoma	*DNAJB1–PRKACA* fusion	Molecularly defined variants of common cancer
Tubular carcinoma of the breast	..	Common cancer (low-grade breast cancer)
Transitional cell carcinoma of the ovary	..	Common cancer (high-grade carcinoma of the ovary)

*Previously known as *YWHAE–FAM22A/B* fusion.

Table 3: **Post-genomics classification of cancers previously classed as rare histological variants of common cancers**

	Pathognomonic mutation	Post-genomics classification
Endometrial cancer	*POLE*	Molecularly defined subtype of common cancer
Breast cancer	*ERBB2* amplification	Molecularly defined subtype of common cancer
High-grade serous ovarian cancer	*BRCA1, BRCA2*	Molecularly defined subtype of common cancer
Non-small-cell lung cancers	*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)*

*Although a proportion of prostate cancers and high-grade serous ovarian cancers are associated with either *TMPRSS2–ERG* or TP53 mutations, respectively, these tumours have not been reclassified as molecularly defined subtypes of common cancer because there are no observable differences between tumours with the specified molecular changes and those without in terms of clinical course or treatment options.

Table 4: **Post-genomics classification of cancers previously classed as common**

In 2007, Soda and colleagues[69] showed the presence of *EML4–ALK* fusions in NSCLCs, and that this fusion was necessary for transformation. The fusion was subsequently shown to be present in 2–7% of NSCLCs,[70] most of which are negative for *EGFR* mutations.[71] This discovery led to the therapeutic assessment of ALK inhibitors, which were associated with an estimated 6-month probability of progression-free survival of 72% (compared with 27·2% estimated from a meta-analysis of patients with similar tumours who were given second-line multidrug chemotherapy) in patients whose NSCLC harbours the *EML4–ALK* fusion.[72,73] Adenocarcinomas of the lung are now generally classified on the basis of their so-called actionable mutations, rather than morphological correlates.[74]

Large-scale consortium-driven genomic analyses are resulting in increasing numbers of molecular subgroups being distinguished from common cancers.[17–19] This multiplicity of mutation-defined subgroupings is exemplified by The Cancer Genome Atlas's comprehensive integrated genomics analysis of 373 endometrial tumours.[18] A molecular classification scheme emerged from this analysis that separates endometrial tumours into four groups that correlate with survival. One of these groups, the *POLE* ultramutated group, was associated with improved progression-free survival compared with the other three groups, despite having a histological appearance that 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.[75–79] Whether these cancers have an indolent natural history or are ultraresponders to standard therapy is not yet known. *POLE*-mutated endometrial cancers account for around 10% of all endometrial cancers, and are rapidly becoming acknowledged as a molecularly distinct subset of endometrial cancer.[80]

Cell context in classification of rare cancers

In addition to the presence of characteristic tumour mutations, the cellular context of these mutations is as important when determining behaviour of tumours because some molecular changes seem to drive transformation only in a particular cell type. FOXL2 expression is essentially restricted to female gonadal stroma, and thus the pathogenetic Cys134Trp *FOXL2* mutation in granulosa cells is oncogenic. Similarly, *DICER1* mutations are uncommon in cancer with the exception of childhood and adolescent cancers, particularly those with embryonic features, such as non-epithelial ovarian tumours and pleuropulmonary blastomas.[14,81] This pattern is perhaps unsurprising, since *DICER1* mutations shift miRNA targeting so that all 5p strand targeting is eliminated while 3p targeting is maintained[13] and 3p miRNAs tend to be dominant in primitive and embryonic cells.

A third example of the importance of cellular context is ovararian hypercalcaemic small-cell tumours. Roughly a third of patients with these tumours do not express both BRG1 and BRM proteins—the two ATPases of the SWI/SNF chromatin remodelling complex that can make up the catalytic core. Small-cell tumours of the ovary hypercalcaemic type seem to be the only tumour that can withstand loss of both of these ATPases.[82] BRM has been described as a synthetic lethal target in other BRG1-deficient cancers, such as lung adenocarcinomas.[83]

Accounting for context is especially important because discoveries of tumour-specific mutations could lead to repurposing of existing treatments, which happened with the tyrosine-kinase receptor inhibitor, imatinib. Imatinib was initially used to treat *BCR–ABL*-positive chronic myelogenous leukaemia, but was shown to be effective against gastrointestinal stromal tumours, which are characterised by *KIT* and *PDGFRA* mutations.

However, targeting the same mutation in different tumour types does not always yield the expected result. For example, vemurafenib, a BRAF inhibitor initially developed to treat patients with melanomas harbouring the $BRAF^{V600E}$ mutation, generated great interest as a potential treatment for patients with colorectal cancer (figure 2) because The Cancer Genome Atlas had shown that roughly 7% of colorectal cancers have this *BRAF* mutation. However, these tumours are also hypermutated (ie, they contain many mutations in other genes),[17] and these other mutations could change the effectiveness of vemurafenib. Furthermore, one study has shown that in-vitro colorectal cancer cells with $BRAF^{V600E}$ mutations seem to have escape mechanisms, such as activation of EGFR, to maintain proliferation of $BRAF^{V600E}$-mutated vemurafenib-resistant colorectal cells.[84] This finding has been substantiated by a study[85] in 21 patients with metastatic colorectal cancer with the $BRAF^{V600E}$ mutation in whom vemurafenib treatment was not associated with a meaningful clinical benefit. Therefore, in the context of colorectal cancer, BRAF inhibition might be more successful when combined with EGFR suppression,[86] or inhibition of other pathways including the PI3K/AKT or MEK pathways.[87]

Developing therapies for rare cancers

Advances in cancer biology and genomic technology have not only led to the definition of various molecularly defined rare cancers, but also are reshaping the focus and practice of drug development. Molecular alterations identified in rare cancers can help with diagnosis and also represent potential treatment targets. However, diagnostic entities are evolving rapidly, making consistent case identification difficult and confounding attempts at systematic data collection. Molecular subclassification can be further extended to include host factors such as expression of immune markers and cell infiltrates, which are of great interest because of the emergence of immunotherapies.

Immunotherapy represents a rich avenue of cancer drug development and efforts are largely directed at drugs that block negative regulators of T-cell immunity, such as CTLA-4 and PD-1. Promising results with this type of treatment have been reported in patients with renal cell cancers, NSCLCs, and melanoma, but the ability to predict response remains elusive.[88–91] The use of tumour-infiltrating lymphocytes, which was first shown to lead to tumour regression in patients with melanoma,[92] is also a potentially effective therapy for patients with metastatic synovial sarcoma expressing the NY-ESO-1 antigen.[93] This trial showed that four of six patients with synovial sarcoma given autologous T cells engineered to express T-cell receptors that recognise the NY-ESO-1 antigen had objective partial responses, with one lasting 18 months. This antigen is aberrantly expressed in around 80% of synovial sarcomas, but also in metastatic melanoma, breast, prostate, thyroid, and ovarian cancers, suggesting that this type of immunotherapy could have wide-ranging applications.

Tumour-specific DNA alterations that give rise to novel protein sequences can produce antigens, known as neoantigens, which are not found in the normal genome. Although not all mutations result in the production of neoantigens, evidence suggests that a higher number of mutations or mutational load is associated with increased neoantigen production.[94,95] Many rare cancers, such as adult granulosa cell tumours and small-cell tumours of the ovary hypercalcaemic type, have low mutational loads and seem to elicit minimum host immune responses. However, mutational load alone cannot predict immune response, and the results of some studies suggest that specific mutations are associated with neoantigen production and immune response. For example, mutations predicted to be accessible to T-cell antigen receptors are more likely to be immunogenic.[96] Another example of a specific immunogenic alteration has been noted in primary mediastinal lymohomas, which express recurrent gene fusions implicating the MHC class 2 transactivator CIITA, leading to overexpression of PD-1 ligand, which affects antitumour responses.[97] Mutations that are probably important to immune response in several cancer types are more often passenger, rather than driver, mutations, and thus targeting these mutations alone might not be sufficient for a clinical response.[94,95,97,98] Although the application of immunotherapy to rare cancers has shown some early promise,[92] the full extent of how immunotherapy can be used has yet to be determined. Development of drugs based on mutations that drive tumourigenesis continues to be important, irrespective of whether the driver mutation is present in a rare or common cancer, because many of these drugs can be repurposed. Crizotinib, an inhibitor of the ALK and MET tyrosine kinases, was initially developed in lymphoma and sarcoma,[99,100] but with the recognition that NSCLCs also have *ALK* fusions, it has been applied to this tumour type with great success.

Compelling reasons exist for trials of treatments for rare tumours related to unmet medical need. Moreover, rare tumours could have disease-defining oncogenic driver mutations that are also present in other cancers for which targeted treatments exist. However, there are specific challenges to mounting trials in the rare cancer setting, related to the low incidence of rare cancers, which can result in low accrual and hence higher costs. International collaborations are one way to sidestep these issues but are associated with high costs and complexity. The International Rare Cancers Initiative was set up to address these challenges.[15,101] It is a joint initiative of Cancer Research UK, the UK National Institute for Health Research Clinical Research Network: Cancer, the US National Cancer Institute, the European Organisation for Research and Treatment of Cancer, the Institut National du Cancer, and the National Cancer Institute Canada Clinical Trials Group. The International Rare Cancers Initiatiave helps with the development of international clinical trials for patients with rare cancers by promoting meetings of researchers to develop priority questions, address design issues, and ease execution. Along with other groups, it has promoted novel designs, including multicohort and adaptive designs, to maximise scientific knowledge gained and trial efficiency. At the outset, ten rare cancers were selected and have formed the core activities of the International Rare Cancers Initiative. These efforts, along with development of drugs by pharmaceutical companies that target molecular alterations present in rare cancers, such as *ALK* fusions in lymphoma and sarcoma targeted by crizotinib,[99,100] and support from funding agencies to study rare cancers, could affect how common cancers are divided into molecularly defined subgroups and improve treatment options available to patients with rare tumours.

Because of the importance of cell context in determination of the pathogenicity and targetability of mutations, potential treatments should be tried in cell context-specific model systems before testing in patients. This tactic has led to successes in the past—eg, tenosynovial giant-cell tumours, which were shown to have translocations that result in overexpression of *CSF1*.[102] Although imatinib, which is reported to inhibit the CSF1 receptor, was recognised as a potential treatment for this cancer, design of preclinical studies was hampered by the absence of appropriate model systems. To address this issue, a xenograft model of tenosynovial giant-cell tumours was developed to test the efficacy of imatinib,[103] which provided the rationale for a subsequent trial[104] in patients showing proof of concept for targeting the CSF1 receptor with imatinib mesylate. These results prompted a phase 1 trial[105] of a selective CSF1 receptor inhibitor in patients with tenosynovial giant-cell tumours, which produced significant regressions in tumour volume, with an overall tumour response of 52%. These results are better than the response of 19% reported in a phase 2 trial of imatinib[106] in 27 patients, and suggest a potential therapeutic option in patients in

Search strategy and selection criteria

We searched for published articles that related to the tumour types discussed in this Series paper, using the names of the tumours as search terms, either alone or in combination with the drug names or gene names discussed. We restricted our searches to articles in English, but did not restrict the dates searched because we were interested in how views about the tumour types discussed have changed with time.

whom surgery is not feasible or would result in substantial functional impairment, because previously there was no approved systemic therapy for these patients. Thus, the development of such preclinical models, when absent, should be a research priority.

In addition to forming consortia, the clinical research community has generated novel trial designs including multiphase, multigroup adaptive umbrella and basket trials with several defined cohorts for the testing of targeted therapies (addressed in detail in another Review[106] in this Series). Such trials increase efficiency by providing opportunities to assess several drugs simultaneously within cohorts of patients with histologically and molecularly defined cancers. The cohorts can be modified with time depending on the drugs' activities. Regulators and funders of clinical trials seem to be open to novel trial designs to speed up assessment and time to approval, and willing to accept post-marketing assessments to generate additional safety and effectiveness data.

Conclusion

When it comes to cancer taxonomy, rare is the new common in the post-genomics era. Many cancers derived from unusual histological origins are now understood to be histomorphological entities often with pathognomonic mutations. Molecular analysis—particularly genomic analysis—is revealing an ever-expanding number of rare molecular subclasses of the more common cancers, which is leading to a more objective classification of tumour types. Therapies targeted at specific molecular events, either in rare or common cancers, have the potential to be repurposed. But repurposing should be done with caution and with initial trials in appropriate preclinical models. As knowledge continues to expand, it will be important to remember that, for molecular subclassification to be embraced, it has to be clinically relevant.

Genomic assessments can lead to the discovery of features that can be rapidly translated into diagnostics and monitoring strategies, but the development of treatment approaches for cancers in which mutational events have been identified also necessitates cell-context-specific model systems for rare cancers, which perhaps should be a focus for future research. Although molecular discoveries have intrinsic value for patients with these rare cancers, they could also lead to more generic strategies to improve management of the ever-increasing number of clinically relevant molecularly defined subgroups of common cancers. Consideration of cell context is crucial when repurposing targeted agents designed for common cancers in the rare setting.

Although clinical trials in rare cancers have historically been difficult because of low numbers of cases, improved identification of these rare entities, and flexibility and innovation in trial design makes them now easier to achieve. Ideally, regulatory authorities working with each other to develop common approaches to the review of trials that recognises the challenges of completing trials in rare cancer settings, and providing means to capture outcomes of patients after approval should lead to better treatment options for patients with rare cancer.

Contributors

All authors drafted the outline, did the search of published work, and wrote and edited this Series paper.

Declaration of interests

JED has received grant support from Pfizer. DGH is chief medical officer and founder of Contetual Genomics. NB and CBG declare no competing interests.

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