RARECARE
Surveillance of Rare Cancers in Europe

**RATIONALE & QUESTIONS FOR CONSENSUS**

**This effort aims at providing a list of rare tumours that are clinically meaningful. It is based on single tumour entities as coded by the ICD-O classification. However, these have pathologic basis but then they need to be grouped in order to have clinical meaning. So this list is first a list of tumours both frequent and rare. They have been grouped into three layers: families of tumours (tumours with the same referral pattern), tumours defined in a clinically sound way (perceived by clinicians as single diseases), and WHO tumour entities. Any first layer includes different tumours belonging to the second layer and any second layer includes different tumour entities of the third layer. In the list, the first layer is marked with the number 1, the second layer with 2, and the WHO entities are marked with 3. A threshold for rarity, as artificial as it will always be, may then be identified within this list by say, choosing a cutoff of frequency. We propose a cutoff based on incidence (<6/100,000/year). It would be applicable to all three layers, i.e. families of tumours, tumours entities, and WHO tumours.**

**Incidence is a good indicator of frequency for rare cancers.**
Rare tumours are rare diseases. Problems related to rare diseases apply to rare tumours as well. In principle, rare tumours should be defined the same way as rare diseases. These are defined as those conditions whose prevalence is lower than 50/100,000. However, the natural history of tumours is such that some of them have a higher prevalence and nonetheless are rare and vice versa. Essentially this is due to the fact that life expectancy varies greatly across tumours. Thus prevalence varies substantially depending on life expectancy although life expectancy has obviously nothing to do with frequency. In addition, several tumours with a prevalence below 50/100,000 are not perceived as rare. For these reasons, incidence may be a more useful indicator to select a threshold for rarity in the case of tumours as opposed to non-neoplastic diseases. It should be clear however that the conventional definition of rare diseases has regulatory implications, including those on orphan drugs. In addition, evolution of therapies may well affect the definition. For example, if anticancer therapies could actually be delivered in a chronic way overcoming the currently limiting factor of tumor resistance, prevalence would become a much more suitable indicator of frequency. At the moment this is not the case although an evolution towards more chronic anti-cancer therapies is in place..

**Any threshold for rarity is artificial.**
By definition, rare diseases are problematic because of their frequency and this is why their definition should only be affected by indicators of frequency. In fact, patients with rare diseases can suffer discriminations because of their low number. Economies of scale cannot be made, there is not enough market for drugs, benefits in outcomes cannot be demonstrated through conventional studies. All these have to do with their low numbers. Thus, a disease is rare when its frequency constitutes a problem per se. However, frequency is not the only problem: some diseases may well be problematic because they are complex to treat or because they constitute an unmet clinical need. Public policy measures should take into account these factors in addition to frequency as rules on orphan drugs do. Thus, even the definition of rare diseases can well be integrated by other attributes. It is just for simplicity and clarity that this list of rare tumours is only based on frequency. An incidence threshold rate may be selected to draw a line between frequent conditions and entities that are considered to be rare inasmuch as they are problematic due to their low frequency. One should always be aware that whatever the line, it is artificial and thus to be used with flexibility.

**This list is based on standard disease classification.**
Disease entity (i.e., its nosographic label) is just an attribute of any clinical presentation. In addition to being affected by a given tumour entity, a patient will present with say a stage of disease which along with his/her sex, age, heritage and several other factors (including concurrent diseases) will eventually determine treatment. In the era of molecular targeted therapies, the molecular profile will be relevant as well. It follows that innumerable clinical presentations which may constitute rare occurrences even when the tumor entity is frequent, whatever the definition. This list can only be based on tumor entities simply because all the other factors which can make a case rare are innumerable. By the way, disease entities themselves are more and more defined on the basis of other features in addition to conventional pathologic aspects namely molecular characteristics. The choice has been

made to simply follow existing tumour classifications. Any list of rare tumours will always be a subset of a standard list of tumours. International agencies that presides over such classifications constantly updating them genetic and molecular profile is more and more relevant to tumour partitioning in such classifications. This list is based on the ICD-O (3rd version) classification inasmuch as this is the worldwide recognized classification of tumours.

**Tumour entities are relevant for clinical decision-making and clinical research while families of tumours are relevant for organization of health care.**

In essence, a rare tumour will be problematic per se, i.e. due to its low frequency under two perspectives, the perspective of clinical decision-making and the perspective of organization of health care. Clinical decision-making is more problematic in the case of a rare tumour because clinical studies on that tumour will be more difficult to do so the quality of available evidence tends to be limited. Under this perspective, a liposarcoma or a bronchioloalveolar lung carcinoma are alike because the feasibility of clinical studies on both conditions is similarly affected by their similarly low frequency. On the other hand, organization of health care is more problematic in the case of a rare tumour because the direct clinical expertise of any community oncologist will be limited in comparison to frequent tumours so some kind of centralized patient referral needs to be implemented (towards centers, or networks, of excellence). Under this perspective however, a liposarcoma or a bronchioloalveolar lung carcinoma are not alike because the former belongs to a family of tumours which are rare as such, while the latter is a lung tumour i.e. it belongs to a family of frequent tumours. Any community oncologist deals everyday with lung tumours and will be aware of bronchioloalveolar carcinoma while this will not be the case for any sarcoma. In fact, centralized patient referral is generally recommended for sarcomas but not for lung tumours. Therefore, under the clinical decision-making perspective, tumour partitioning needs to be as detailed as required by the diversity of treatments. On the contrary, under the health care organization perspective, the level of detail may be lower. A bronchioloalveolar carcinoma will be rare under the clinical decision-making but not the health care organization perspective while any sarcoma will be rare under both perspectives.

**This list of rare tumours is hierarchically structured in three layers: 1) families of tumours; 2) clinically meaningful tumours; 3) tumour entities.**

This list is hierarchically structured in three layers, based on various combinations of ICD-O morphology and topography. The first layer denotes the main families of tumours identified according to a consensus-based clinical perspective. This partitioning should be mainly useful for patient referral purposes i.e. it is relevant under the health care organization perspective. A family of tumours generally finds its own referral pattern. The second layer denotes tumours as relevant from the clinical basically the therapeutic, decision-making perspective. This partitioning should be mainly useful for clinical purposes, e.g. for clinical studies, etc. The two layers simply group the ICD-O codes in a clinically sound fashion at a different level of depth. All tumour entities as codified by the current classification of malignant tumours are included and the third layer therefore enlists the WHO (blue book) entities. For each first- and second-layer group of tumour entities and for each third-layer tumour entity, the relevant crude incidence is reported. The incidence rates are calculated from the 70 population based cancer-registries that adhered to the RARECARE project.

**A threshold for rarity is submitted for consensus.**

Any threshold for rarity should be considered as just indicative. By and large for many purposes, tumour families and tumours with an incidence around 5/100,000/year have been considered to be rare enough as to justify special efforts, those required for diseases whose frequency is low. This means that all tumours belonging to families (first layer) whose incidence is less than 6/100,000/year would be regarded as rare. Health organization measures should be taken for them, such as patient referral to reference networks or centers. In addition, they imply special problems for clinical decision-making and clinical research. Outside these families of rare tumours, single tumours (second layer) whose incidence is below that threshold look rare as far as clinical decision-making and clinical research is concerned.

**Questions for consensus.**

1. **Is the list of tumours acceptable, as means to single out families of tumours having the same referral pattern (first layer), and tumour types perceived by clinicians as single diseases (second layer)?**
2. **Is the incidence threshold of <6/100,000/year acceptable to identify families of tumours which are rare for health organization, and tumour kinds which are rare for the clinical decision-making and clinical studies?**