E. 6. Quality Standards of Samples

Generating collections of high quality tumor samples is likely to be a major challenge of the ICGC. Committed partners and funding agencies will need to invest substantial effort and funds. General guidelines were developed by the Quality Standards of Samples Working Group that could apply to a broad spectrum of cancer subtypes displaying a wide variety of histopathological and clinical characteristics. However, optimal standards may differ considerably between the tumor entities.

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<th>POLICY: Every project will adhere to the following four recommendations:</th>
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<td>1. A committee of clinical and pathology experts (with representation from different institutions) will be needed to draft and oversee the specific guidelines that will apply for every tumor type or sub-type. These guidelines will have to be made available to all members of the Consortium, and users of the data.</td>
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<td>2. Tumor types should be defined using the existing international standards of the WHO (including ICD-10 and ICD-O). If novel molecular subtypes are studied, these should be defined with sufficient detail.</td>
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<td>3. All samples will have to be reviewed by two or more reference pathologists. This assessment will need to be performed on stained sections of the very same tissue piece from which biomolecules will be purified. Histological examination has to be documented and respective optical images have to be stored and made available i) to those studying the given samples and ii) on a dedicated web-page for open access. The use of virtual slides is recommended.</td>
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<td>4. Patient-matched control samples, representative for the germline genome, are mandatory to discern “somatic” from “inherited” mutations. For solid tumors, the mononuclear cell fraction from peripheral blood is the ideal source, while for hematological malignancies skin biopsies or (lymphocytes from patients in remission) are recommended.</td>
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Box 4. Guidelines regarding the quality standards of samples

- In the initial projects of the ICGC, it is recommended to begin with tumor entities (and samples) that are the most “homogeneous”;
- In the initial projects of the ICGC, tumor samples should be untreated malignancies, i.e., in general primary and not relapsed, preferably from a single anatomical site of origin and representing a single histological type/subtype (and if feasible, a single histopathologic grade);
- Tumor sample inclusion criteria should require at least 80% of each sample to be composed of viable-appearing tumor cells on histological assessment and less than 20% necrotic cells or normal cells such as inflammatory, immune, or stromal cells, or even pre-malignant (dysplastic) cells. In some tumor types, it might be necessary to adopt a less stringent criterion by the expert panel, but if the tumor cell content is not substantially higher than 60%, physical enrichment procedures need to be considered;
- Histological examination will have to be documented and respective optical images have to be stored and made available to those studying the given tumor entity. Specifically the degree of 1) necrosis; 2) debris; 3) inflammatory tissue; and 4) fibrosis are to be assessed;
- Standard Operating Procedures (SOPs) for freezing samples will be those established by WHO/IARC (2007);
- As a basis for the exchange of tissue specimen between countries with different national regulations that need to be respected, a coordinating rule has been formulated on the basis of the ‘home-country principle’;
- Ideally, 200 mg of solid tissue or 10 million flow-sorted cells (i.e., blood tumors) will be available for each sample. If microdissection is necessary, the number of required cells is still unknown. This aspect needs to be revisited at a later time point;
- Although many types of macromolecules should be isolated, priority should be given to the isolation of high quality DNA (which is also valid for some epigenomic analyses). Isolation of high quality RNA is also recommended;
- The quality of the isolated classes of macromolecules needs to be controlled by standardized procedures used by all members of the ICGC. The choice of these tests will be defined by an ICGC working group;
- Controls for transcriptomic and epigenomic analyses may require site-matched tissue control samples. This aspect must be dealt with in the recommendations of the tumor-specific expert panel;
- The minimum set of clinical variables that must be collected for each tumor sample are:
  - General data (DOB, age, gender, date of diagnosis, presence of metastases, etc.);
  - Diagnostic data (biochemical, cytogenetic, immunophenotypic and other data);
- Acquisition of follow-up information is highly recommended for subsequent interpretation of ICGC data and clinical correlations:
  - Therapies after removal of malignant cells;
  - Response to therapy (EFS, CR, OS, definition of end points of trials).