NCCP Framework for Decision Making for Cancer Molecular Diagnostic Tests in the Irish Molecular Pathology Service

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This document has been produced by the National Cancer Control Programme (NCCP) to support the current and future development and evaluation of cancer molecular diagnostics testing in Ireland.

If you have any queries regarding this Framework, please contact: National Cancer Control Programme oncologydrugs@cancercontrol.ie / 01 8287150

Further details can be found at http://www.hse.ie/eng/services/list/5/cancer/

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Acknowledgement

This framework is adapted with permission from the NHS Scotland document entitled “A Framework for Decision Making for Tests in the Scottish Molecular Pathology Service”(National Health Service Scotland, 2020)

Contents

1. Introduction

This document provides a framework for ensuring that decisions relating to the classification and declassification of cancer molecular diagnostics tests in the Irish molecular pathology service, as it relates to oncological and haematological malignancies in the Irish public health service, are reasonable, transparent and justifiable.

The framework is used to appraise the evidence on the efficacy and effectiveness of tests. Tests will be assessed against set criteria. The Cancer Molecular Diagnostics Advisory Group will make recommendations to the National Cancer Control Programme (NCCP) on the clinical validity, analytical validity and clinical utility of tests. These recommendations inform the NCCP on deciding which tests should be supported on a national basis and included in the NCCP National Genomic Test Directory for Cancer.

2. Irish Molecular Pathology Service

Molecular diagnostics, allows certain cancers to be treated based on their genetic profile and can be used to determine the success of cancer treatment regimens for particular cancers. Cancer molecular diagnostics testing is currently provided in a number of public hospital locations in Ireland. At present the NCCP partially funds cancer molecular diagnostics testing predictive for SACT in two hospitals. Limited testing takes place at other hospital sites and/or external commercial service providers are used by some hospitals.

The National Cancer Strategy (Department of Health, 2017) acknowledged that an accurate pathological diagnosis was at the core of multidisciplinary management of any patient diagnosed with cancer but that there was largely a lack of direction in regard to molecular cancer diagnostics in Ireland. The strategy recognised that a mechanism was required to determine how well current testing is being performed, where testing should be performed, how effective the service is for patients and clinicians, when tests should be replaced and when new tests should be considered.

3. Molecular Pathology Definition

In part due to the rapidly evolving nature of these specialist scientific tests, there is no universally agreed definition of molecular pathology. It is primarily related to testing undertaken for “the molecular pathology of acquired disease and primarily the areas of cancer diagnosis, predictive and prognostic testing. For the Haematological malignancies the focus also included molecular assessments of Bone Marrow transplantation and minimal residual disease.”

The Cancer Molecular Diagnostic Advisory Group definition of molecular pathology in cancer is:

“The use of molecular biomarkers in the diagnosis, prognosis, disease monitoring and treatment stratification of human cancers”

Molecular pathology is widely recognised as the study of biochemical and biophysical cellular mechanisms as the basic factors in disease. This can encompass a wide range of genes and diseases and may include DNA from humans, viruses, bacteria and microbiology.

Molecular pathology for the purposes of this framework is restricted to the human genome and genetic markers or their surrogates for malignant tumours (cancer) primarily for the purpose of informing decision making regarding optimal treatment approaches.

3.1 Types of Tests

A molecular pathology test is used to identify molecular biomarkers in the diagnosis, prognosis, disease monitoring and treatment stratification of human neoplastic conditions[1].

3.1.1 Diagnosis

The test is used in the diagnosis of a neoplasm or to aid in the differential diagnosis. It may be used for exclusion purposes as well as confirmation e.g. the use of FOXO1 in the differential diagnosis of alveolar versus embryonic rhabdomyosarcoma or BIRC3-MALT1 in the diagnosis of MALT type lymphomas.

3.1.2 Prognosis

The test gives an indication to the likely long term outcome for the patient and may involve the likely treatment response and/or survival on standard therapies. This is usually based on a comparison of the outcome when measured against the expected outcome for the same neoplasm with a normal genome content (as defined by current testing procedures) and often published as part of a clinical trial report.

3.1.3 Disease monitoring

The test may be used to monitor the disease status in the patient. Once an aberration has been identified, it may be possible to use this to monitor the disease status in the patient. Depending on the neoplasm, this may require a defined sequential monitoring of samples or when there is a defined clinical change in the patient (e.g. clinical relapse, disease progression). Such examples may include the monitoring of disease specific somatic mutations in the IgH gene in cases of ALL or the FISH analyses of cells from urine sediment in the case of bladder cancer.

3.1.4 Treatment Stratification

The test may be used to indicate whether a particular course of treatment would be suitable for a patient or not. The test may be used both to include as well as exclude a possible therapy in a patient. Such testing would include ERBB2 testing in breast cancer to determine suitability for Herceptin therapy or not, or PML-RARA testing in acute promyelocytic leukaemia to determine suitability for ATRA/arsenic therapy.

Although diagnosis, prognosis, disease monitoring and treatment stratification have been listed separately, some tests could be categorised in more than one of these groupings, for example a BCR-ABL1 positive result could be used in diagnosis [CML, ALL or AML], disease monitoring [(RT-q) PCR for minimal residual disease] or treatment stratification [imatinib or similar tyrosine kinase inhibitor (TKI)] and prognosis [a BCR-ABL1 positive individual on a TKI has a good prognosis].

4. National Cancer Control Programme

The NCCP was established in 2007 with a remit to lead and implement the change management process required to reorganise cancer services and set up a system of quality assurance and oversight designed to improve the care and outcomes for cancer patients. It has adopted a population based approach to planning and aims to integrate all aspects of cancer care and oversee all activities.

The 2017 National Cancer Strategy (Department of Health, 2017) identified that the cancer molecular

[1] A human neoplastic condition is abnormal mass of tissue resulting from an abnormal proliferation of cells. It usually causes a lump or tumour (but not always). Neoplasms may be benign, pre-malignant (carcinoma in situ) or malignant (cancer).

diagnostics, predictive for SACT service in Ireland was poorly organised, fragmented and required development.

The National Cancer Strategy (Department of Health, 2017) made two specific recommendations on the future of cancer molecular diagnostic services in Ireland:

- **Rec 17**. The NCCP will appoint a National Lead for Cancer Molecular diagnostics for solid and liquid malignancies.
- **Rec 18.** The NCCP will establish a steering group for Cancer Molecular diagnostics, chaired by the National Lead. This steering Group will set out the framework for the organisation, location and delivery of cancer molecular diagnostic services.

The NCCP established the Cancer Molecular Diagnostics (drugs) Advisory Group in 2017 comprising of representatives from pathology, haematology, medical oncology, genetics and laboratory science to advise on the relevant cancer molecular diagnostic testing requirements. The focus of this group was molecular diagnostics tests predictive for drug use and the NCCP Framework for Decision Making for Tests (Predictive for Systemic Anti-Cancer Therapy Treatment) in the Irish Molecular Pathology Service was developed. The scope of this group was extended in 2022 to oversee cancer molecular diagnostic and prognostic testing as well as providing leadership expertise in the area of molecular diagnostics and the Terms of Reference are available in Appendix1.

This framework for cancer molecular diagnostic tests aims to meet the recommendations of the National Cancer Strategy.

The goals and actions of the group are:

- Provide advice to the NCCP on cancer molecular testing requirements to identify molecular biomarkers for diagnosis, prognosis, disease monitoring, treatment options and treatment stratification. This work will align with the HSE National Genetics and Genomics Strategy.
- Contribute to the development of a NCCP National Genomics Test Directory for Cancer in collaboration with the NCCP SACT Clinical Advisory Groups and Tumour Leads as appropriate
- Oversee an annual review or rolling review of the NCCP National Genomics Test Directory for Cancer
- Evaluate new test applications for inclusion in the Test Directory as well as any proposals to alter the eligibility criteria, constituent tests or technology for existing tests
- Facilitate the development of a collaborative network among laboratories to (1) enable collaboration (2) advance knowledge (3) assist in the interpretation of variants (4) support validation of molecular diagnostic tests and (5) develop consistent approaches to pipeline workflows
- Contribute to the continuous improvement of the molecular diagnostic service with a specific focus on service development and national standardisation, to meet the growing needs of the service and ensure timely and equitable access to the service.
- Contribute to the monitoring of the cancer molecular diagnostics including agreement of any key performance indicators.
- Advise and collaborate with other NCCP committees as appropriate, where service interests coincide.
- Advise on the implementation of recommendations from national clinical guidelines which relate to molecular diagnostics for cancer.
- Provide a forum for collaborative discussion and decision-making on which tests will be provided in Ireland, in which laboratories and the priorities for introducing new tests.

- Identify best practice to ensure that everyone in Ireland has access to the same high quality and timeliness of molecular pathology tests, regardless of geographical location.
- Review annual activity, past trends and project forward likely future trends in activity of molecular pathology laboratory testing in Ireland.
- Horizon scan and plan for sustainable services for the future.

4.1 Out of Scope

Matters relating to funding of the service are outside the scope of this group and will continue to be managed under the existing service planning and monitoring model.

Testing relating to clinical trials will not be included within the NCCP National Test Directory

The requirements for molecular testing for hereditary cancers except those predictive for drug use are outside the scope of this group.

5. Principles of Decision Making

The NCCP Molecular Diagnostics Advisory Group evaluates current and future molecular diagnostic requirements as related to cancer and advise on the clinical validity of tests that should be provided on a national basis. They may advise on the number of Irish laboratories in which tests will be carried out in. The NCCP executive committee will then be advised accordingly.

As outlined in the National Cancer Strategy 2017 (Department of Health, 2017) the NCCP's Cancer Molecular Diagnostic Advisory Group identified the need for a framework outlining a decision making process to agree to appropriate tests ensuring molecular diagnostics for cancer is carried out in a coordinated and standardised way. This includes the development of a Test proposal form (Appendix 2) to be completed.

It was agreed that:

- The framework will be applied retrospectively to the tests currently undertaken in Ireland
- Tests that are recommended for inclusion will inform service planning.[2]

The HSE Framework for Improving Quality in our Health Service, Part 1: Introducing the Framework (Health Service Executive, 2016) described six standards for providing a safe, high quality and integrated health service. These standards are applicable to the development of the Irish cancer molecular diagnostics service in ensuring a quality service is developed and maintained. A robust national framework will help to ensure that cancer molecular diagnostics services meet these standards.

5.1 Person and family engagement

In a person centred service, providers engage and listen to all their service users and support them to play a part in how the service is run. The service is focused on working towards the needs of the service users rather than on what is convenient for the service provider.

5.2 Leadership for quality

This involves seeking out and obtaining all opportunities to demonstrate a commitment to building a culture of quality, seeking evidence of that quality and focusing on enabling a safe and consistent

[2] Testing will continue to be funded under the current funding model

cancer molecular diagnostics service for the referring clinicians and the patients they refer.

5.3 Governance for quality

This involves having the necessary structures, processes, standards and oversight in place to ensure that a safe, person centred, effective cancer molecular diagnostic service is delivered.

5.4 Measurement for quality

Information and measurement are central to improving quality of care. Analysing data relating to a service provides information that can be used to drive improvements and support assurances on the quality of the cancer molecular diagnostic provided. The advisory group will contribute to the monitoring of cancer molecular diagnostics, including the agreement of any Key Performance Indicators (KPI).

5.5 Use of improved methods

Using improvement methods to enable quality improvements in cancer molecular diagnostic services is fundamental in ensuring new emerging evidence on molecular diagnostics testing is considered and appropriately implemented into practice. This includes standardisation of services which would assist in reducing variation across processes, helping to ensure a sustained quality service.

5.6 Staff engagement

Positive staff engagement is critical to achieving high quality care. This framework will help ensure that appropriate guidance is put in place to support staff in decision making allowing them to engage in a process that informs improvements and facilitates participation in the delivery of quality molecular diagnostics for cancer.

6. Current tests assessed

The current tests recognised by the group and locations of the provision of these tests are listed in Appendix 3.

7. Process for consideration of new tests

7.1 NCCP Molecular Diagnostics Advisory Group

Cancer molecular diagnostics tests will be assessed and evaluated by the Cancer Molecular Diagnostics Advisory Group, who will have responsibility for working to the confines of this framework, using their knowledge in their field of expertise to assess and evaluate the test proposal form, ensuring that all cancer molecular diagnostics tests undertaken are evidence based. If the advisory group endorses the recommendations of introducing a new test, they must decide how the test is implemented across Ireland.

7.2 Laboratory Minimum Standards

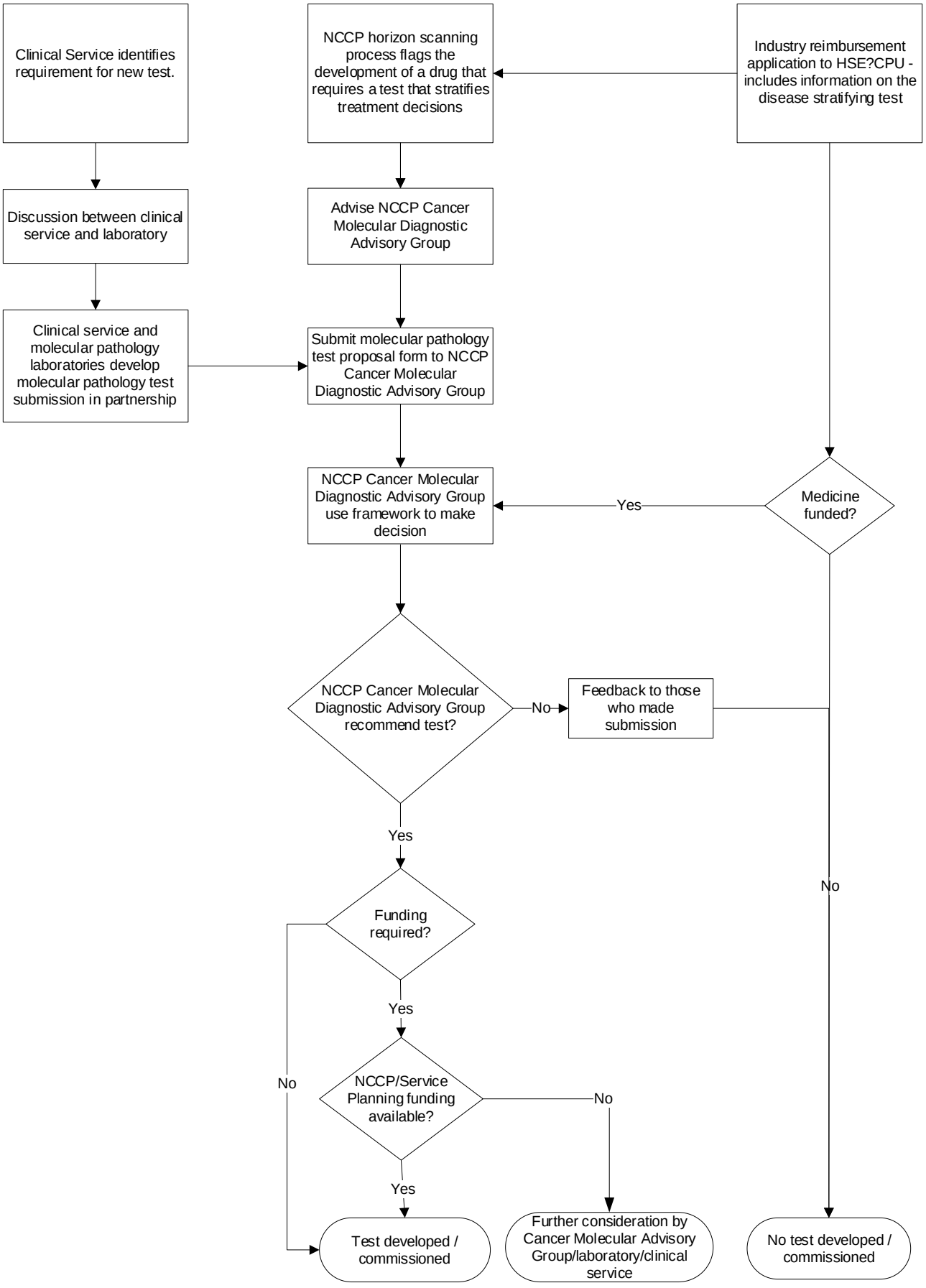
Submissions for inclusion of tests in the national framework will be accepted from laboratories that maintain the following laboratory standards:

- Any proposed test has been fully validated.
- Any proposed test is either currently accredited to ISO15189 standards or an application for accreditation is in progress. Where a test is not already accredited, the validation report should be included with the application
- The Laboratory participates in appropriate national, UK or European external quality assurance schemes, for the particular tests/disorders. The testing laboratory should declare performance history, this should include participation in genotyping plus interpretation schemes where available. Where no such scheme exists, the laboratory should take part in a sample exchange

with another accredited medical testing laboratory

- The Laboratory meets agreed turnaround times, as dictated by relevant clinical standards
- The Laboratory collects data for audit, evaluation and monitoring purposes
- The Laboratory demonstrates that it provides a reliable service, including planning for staffing issues and technical problems
- The Laboratory supports clinical audit and development, and preferably has an active programme of research

7.3 Process and Governance Structure



7.4 Reporting Structure

The NCCP Molecular Diagnostics Advisory Group will consider the submission and liaise with relevant stakeholders with regards to current and future cancer molecular diagnostics and consider the resource implications associated with the test and develop options on how the test can be implemented across Ireland in the most clinically and cost effective manner. The NCCP Molecular Diagnostics Advisory Group reports to the NCCP National Executive.

7.5 Appeals process

In cases where a test is not recommended, feedback on the reasons will be provided to those who made the submission. Details on the appeals process can be obtained from the NCCP Molecular Diagnostics Advisory Group secretariat (oncologydrugs@cancercontrol.ie).

7.6 Principles that the NCCP Molecular Diagnostics Advisory Group works within

Once the NCCP Molecular Diagnostic Advisory Group has recommended a test following the evaluation of the test proposal form, decisions on how many laboratories will do the test will be made by the NCCP executive committee following review of the Advisory Group recommendations.

The test proposal form outlines the reasons for undertaking the test, should additional reasons for undertaking a test be introduced following the original submission, i.e. to inform different treatment decisions. Tests that are recommended for inclusion will inform part of the annual service plan.

If the HSE approve a drug for reimbursement which will require a companion test, a test submission to the NCCP Molecular Diagnostics Advisory Group will be required to allow planning and implementation of the test. This submission should be made sufficiently early in the HSE approval process to ensure availability of the test at time of drug approval.

7.7 Decommissioning Tests

Laboratory activity is monitored and discussed annually at the NCCP Molecular Diagnostics Advisory Group. Should requests for tests cease, this will be discussed with relevant stakeholders; if there is clinical consensus that the test is no longer required, due to different treatment pathways, the NCCP will cease to commission the test.

A test may also be phased out if a new test with superior diagnostic performance is introduced. Review of laboratory activity will include review of laboratory testing pathways, to ensure that the testing pathway of highest quality and greatest efficiency is supported.

7.8 Links with HSE reimbursement process and test manufacturers

The NCCP Molecular Diagnostics Advisory Group will be updated regularly by the NCCP Systemic Therapy Programme with early notification of medicines that are in the reimbursement process or alerted through horizon scanning that will require a companion diagnostic test which will be undertaken by the molecular pathology laboratories.

Appendix 1- Terms of Reference NCCP Molecular Diagnostic Advisory Group

Introduction

Molecular diagnostics allows certain cancers to be treated based on their genetic profile and can be used to determine the success of cancer treatment and in selecting treatment regimes for particular cancers.

The NCCP is establishing a group to advise on the relevant cancer molecular diagnostic testing requirements. The scope of the group covers those tests that are diagnostic, prognostic and predictive for drug treatment.

Goals/Actions

- Provide advice to the NCCP on cancer molecular testing requirements to identify molecular biomarkers for diagnosis, prognosis, disease monitoring, treatment options and treatment stratification. This work will align with the HSE National Genetics and Genomics Strategy.
- Contribute to the development of a NCCP National Genomics Test Directory for Cancer in collaboration with the NCCP SACT Clinical Advisory Groups and Tumour Leads as appropriate
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Chairmanship

The Chair will be appointed by the NCCP National Director.

Membership

Membership of the NCCP Molecular Diagnostics Advisory group will consist of:

- NCCP Clinical Lead for Medical Oncology (or nominee)
- NCCP National Clinical Leads for Haemato-oncology (or nominee)
- Molecular diagnostics service provider
- Irish Haematology Society (IHS) Representative (minimum of 1; additional to NCCP lead)
- Molecular diagnostics service user
- Irish Society of Medical Oncologists (ISMO) Representative (1;additional to NCCP lead)
- A consultant paediatric oncologist
- The Clinical Lead from the National Clinical Care Programme for Pathology
- Faculty of Pathology representative
- Pathology representatives from each of the Designated Cancer Centres reflecting the Regional Health Authorities and CHI
- Consultant Histopathologist(s) representing service providers for solid tumour molecular diagnostics
- Consultant Haematologist representing service providers for haematological molecular diagnostics
- Two clinical scientists
- NCCP Assistant National Director Systemic Therapy Programme
- Chief II Pharmacist (Molecular)

Invited Experts

Experts in a particular area, who are not members of the committee, may be invited to contribute to specific meetings or for specific items at a meeting, as appropriate.

Duration of membership

Current membership of the group is for three years and may be further extended.

Quorum

Minimum of six members, including at least three medical members.

Planned review of Terms of Reference

These should be reviewed and refreshed within 3 years of the date of agreement.

Secretariat

The NCCP will coordinate the group and ensure appropriate administrative support, meeting rooms and teleconferencing facilities. Meetings will be facilitated primarily by teleconference and paperwork will be distributed by email in advance of meetings.

Meeting Frequency

Meetings will be held quarterly but more frequently as required with the agreement of members.

Sub Groups

The Chairperson may decide to establish a subgroup on a specific matter that needs concentrated work with additional expertise from individuals outside of the NCCP Molecular Diagnostics Advisory Group. A TOR will be agreed for any such sub group which will report to the NCCP Molecular Diagnostics Advisory Group.

Reporting relationships

The group will provide updates to the NCCP Executive Team meetings.

Appendix 2 - Test Proposal Form

Supporting document is available in the NCCP.

Appendix 3 - Supporting document is available in the NCCP.

Bibliography

DEPARTMENT OF HEALTH 2017. National Cancer Strategy 2017-2026.

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