Algorithms for molecular testing in solid tumours

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Keywords: brain cancer, endometrium cancer, head and neck cancer, lung cancer, melanoma, molecular tests, NGS, oncology, ovarian cancer, soft tissue tumours, thyroid tumours.

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SUMMARY

In order to advise the Federal Government on the reimbursement of molecular tests related to Personalised Medicine in Oncology, the Commission of Personalised Medicine (ComPerMed), represented by Belgian experts, has developed a methodology to classify molecular testing in oncology. The different molecular tests per cancer type are represented in algorithms and are annotated with a test level reflecting their relevance based on current guidelines, drug approvals and clinical data. The molecular tests are documented with recent literature, guidelines and a brief technical description. This methodology was applied on different solid tumours for which molecular testing is a clear clinical need.

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INTRODUCTION

The clinical management of patients with cancer has become more challenging with the advent of numerous innovative molecular tests giving the opportunity to the care givers to tailor the patient's management by fine-tuning the diagnosis or by predicting the resistance or response to a therapy. In addition, test results may also provide information on prognosis.

In order to advise the Federal Government on the reimbursement of molecular tests related to Personalised Medicine in Oncology, the Belgian Commission of Personalised Medicine (ComPerMed) was created in 2016. This commission includes representatives of all professional organisations directly involved in personalised medicine, including experts from the College of Genetics, the College of Oncology, the Commission of Anatomic Pathology, the Commission of Clinical Biology and different working groups with Belgian oncologists, haematologists, pathologists, clinical biologists, geneticists and other scientists. The ComPerMed is organised in different working groups according to the tumour type.

The ComPerMed advises the Platform Companion Diagnostics (CDx platform) from the Belgian reimbursement agency National Institute for Health and Disability Insurance (NIHDI) or RIZIV/INAMI on decision making related to the reimbursement of diagnostic tests in personalised medicine. The CDx platform, launched in January 2016, aims to evaluate the reimbursement of a molecular test and the corresponding patient management in personalised medicine.

The ComPerMed has set up a methodology in order to systematically evaluate and prioritise, for different tumour types, the molecular tests currently performed in Belgium in clinical routine or in research phase.[1]

METHODOLOGY

The methodology has been previously described and applied for digestive and breast tumours.[2,3] Briefly, for each tumour type, the corresponding working group of the ComPerMed *(Table 1)* started with a systematic evaluation of all molecular tests currently performed in clinical routine in Belgium, taking into account their test utility (diagnostic, prognostic or therapeutic), and then assigned, for each of them, a test level. Three test levels *(Table 2)* were defined, with level 1 representing the highest priority of implementation of the test by the policy makers. These test levels are assigned based on their use in clinical guidelines, expert opinions and on reimbursement rules for drugs in Belgium. This test level scale allows easy implementation of common biomarker testing into clinical practice. Furthermore, it facilitates the development of reimbursement criteria.

In this paper, the methodology has been applied for lung, melanoma, brain, endometrium, ovarian, head and neck, soft tissue, and thyroid tumours.

ALGORITHMS

To design the molecular test algorithms, only tests with a level of 1 or 2A were retained. However, some tests with level 2B were also added to the algorithm if the expert group estimated that they will become a test level 1 or 2A in the near future. For lung, melanoma, brain, endometrium, ovarian, head and neck, soft tissue and thyroid tumours, the different molecular tests used in Belgium are sequentially represented in the shape of algorithms (*Figures 1-8*). These algorithms are published on the ComPerMed website *www.compermed.be/* with additional information, such as tumour incidence (provided by the Belgian Cancer Registry), and, for each molecular test, its utility (diagnostic, prognostic or therapeutic utility), its corresponding test level and a brief technical test description. In case of next generation sequencing (NGS) testing, the genes and regions that have to be analysed at minimum are also described. These algorithms will be reviewed annually. Additional updates of the gene tests are possible when requested by experts.

TABLE 1. ComPerMed expert groups.

Lung tumour experts
Jacques De greve
Rebecca De Pauw
Franceska Dedeurwaerdere
Nicky D'Haene
ChristopheDooms
Liesbeth Ferdinande
Martens Geert
Elke Govaerts
Brigitte Maes
Patrick Pauwels
Myriam Remmelink
Sabine Tejpar
Caroline Van den Broecke
Lieve Vanwalleghem
Karim Vermaelen
Els Wauters
Birgit Weynand

Melanoma tumour experts
Lieve Brochez
Nicky D'Haene
Marjan Garmyn
Martens Geert
Joseph Kerger
Vibeke Kruse
Brigitte Maes
Patrick Pauwels
Sabine Tejpar
Ivo Van den Berghe
Joost van den Oord

Brain tumour experts
Tom Boterberg
Pascale De Paepe
Franceska Dedeurwaerdere
Amelie Dendooven
Nicky D'Haene
Martens Geert
Martin Lammens
Pierre Lefesvre
Brigitte Maes
Patrick Pauwels
Isabelle Salmon
Raf Sciot
Sabine Tejpar
Lien Van De Voorde
Caroline Van den Broecke

Endometrium tumour experts
Hannelore Denys
Nicky D'Haene
Giuseppe Floris
Martens Geert
Thomas Gevaert
Joseph Kerger
Patrick Neven
Patrick Pauwels
Kevin Punie

Endometrium tumour experts (to be continued)
Sabine Tejpar
Koen Van de Vijver
Ivo Van den Berghe
Katrien Vandecasteele
Adriaan Vanderstichele

Ovarian tumour experts
Hannelore Denys
Nicky D'Haene
Giuseppe Floris
Martens Geert
Thomas Gevaert
Joseph Kerger
Patrick Neven
Patrick Pauwels
Kevin Punie
Sabine Tejpar
Koen Van de Vijver
Ivo Van den Berghe
Katrien Vandecasteele
Adriaan Vanderstichele

Head and neck cancer experts
Sylvie Rottey
Nicky D'Haene
Esther Hauben
Yassine Lalami
Martin Lammens
Jean-Pascal Machiels
Patrick Pauwels
Myriam Remmelink
Sabine Tejpar
Lieve Vanwalleghem

Sarcoma experts
David Creytens
Pascale De Paepe
Ramses Forsyth
Lore Lapeire
Pierre Lefesvre
Patrick Pauwels
Raf Sciot
Sabine Tejpar

Thyroid tumour experts
Maria-Christina Burlacu
Giuseppe Costante
Brigitte Decallonne
Nicky D'Haene
Esther Hauben
Martin Lammens
Patrick Pauwels
Isabelle Salmon
Sabine Tejpar
Caroline Van den Broecke
Annick Van den Bruel
Lieve Vanwalleghem

TABLE 2. Test levels.

1	Standard of care biomarker for diagnosis and/or prognosis *
	Biomarker predictive of response or resistance to a reimbursed drug in Belgium for this indication
2A	Recommended standard of care biomarker for diagnosis and/or prognosis +
	Biomarker predictive of response or resistance to an EMA-approved drug for this indication
2B	Biomarker predictive of response or resistance to an EMA-approved drug for another indication or to a drug for which a clinical trial is available for this indication
3	Clinical evidence supporting the biomarker for diagnosis and/or prognosis °Biomarker predictive of response or resistance to (1) a drug for which a clinical trial is not available in this indication or to (2) a compassionate use of drug

** Standard of care: Included in guidelines (WHO…) AND consensus from ComPerMed experts*

+ Recommended standard of care: Clinical evidence AND consensus from ComPerMed experts

° Preliminary evidence and no consensus from ComPerMed experts

CONCLUSION

To conclude, a systematic evaluation of new molecular tests in different cancer types and a clear workflow for an optimal clinical management of patients with cancer are required in order to further improve diagnosis, knowledge of prognosis and treatment in the era of personalized medicine. Test levels have to be used to classify the molecular tests regarding their potential clinical utility. Standard-of-care tests (level 1or 2A) are necessary for the proper management of the cancer patient and therefore require appropriate reimbursement. A regular update of the reimbursement rules is necessary to include molecular tests that reached a higher test level or to cancel reimbursement of tests that are outdated. This will avoid extra costs for laboratories, patients and in the end the community.

Other crucial initiatives are also ongoing to ensure Belgian healthcare quality, such as national quality control assessments of the molecular tests linked with their reimbursements and the development of Belgian guidelines for homogeneous interpretation and reporting of the molecular test results.

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KEY MESSAGES FOR CLINICAL PRACTICE

1. **For an optimal and harmonised management of cancer patients in Belgium, a Commission of Personalised Medicine (ComPerMed) has set up workgroups of Belgian experts, to develop and update molecular testing algorithms.**
2. **This manuscript presents the updated algorithms for the standard-of-care testing of lung, melanoma, brain, endometrium, ovarian, head and neck, soft tissue and thyroid tumour samples.**
3. **A common test level scale allows easy implementation of biomarker testing into clinical practice and facilitates the development of reimbursement criteria.**
4. **Molecular testing algorithms are useful tools to link the molecular test and the therapy reimbursement by the INAMI/RIZIV.**

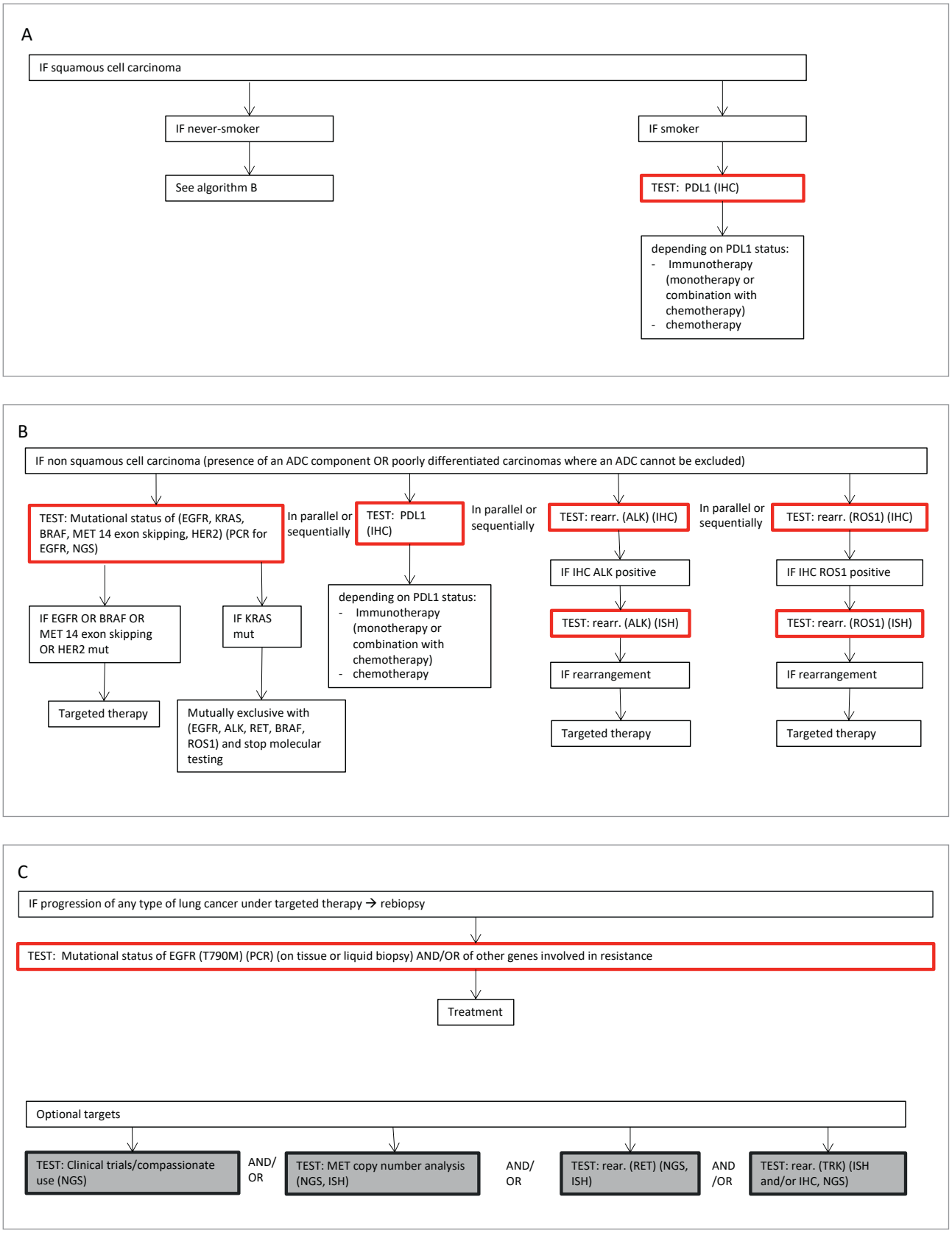


FIGURE 1A-C. Lung cancer algorithms.

Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.

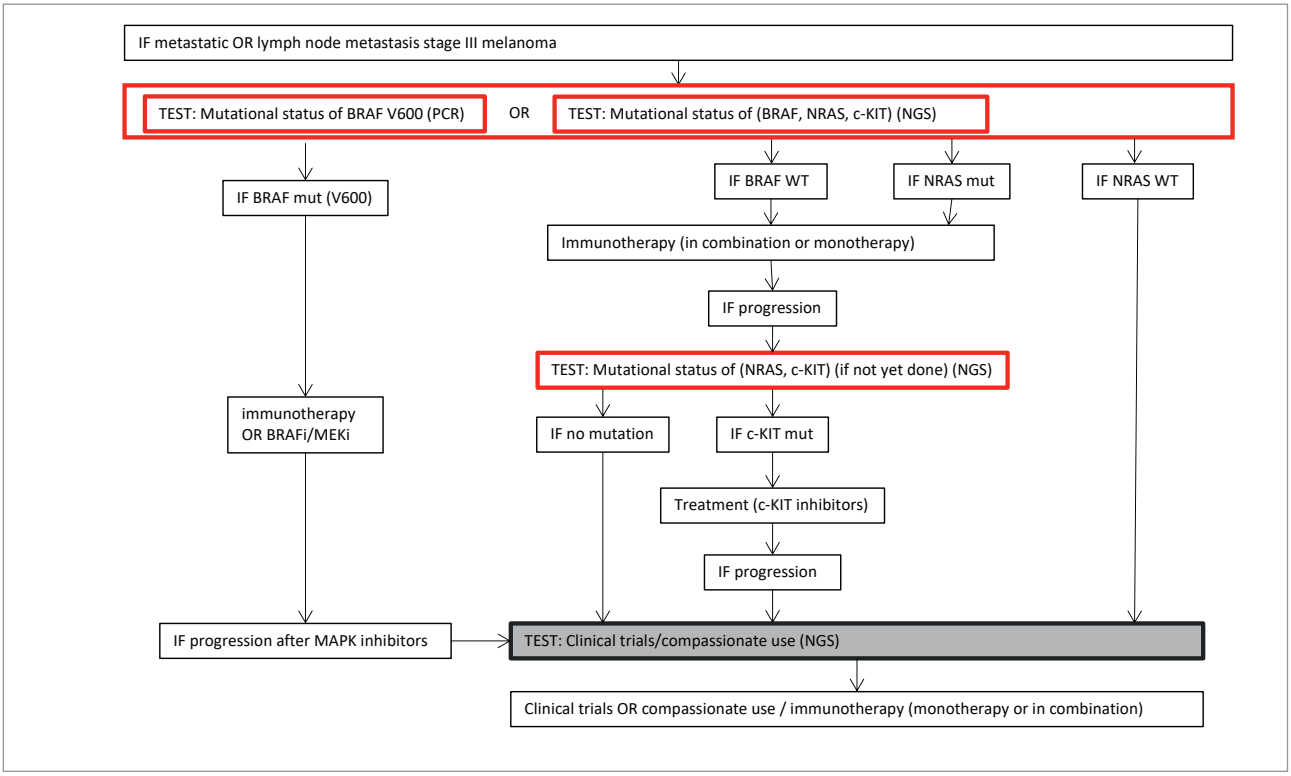
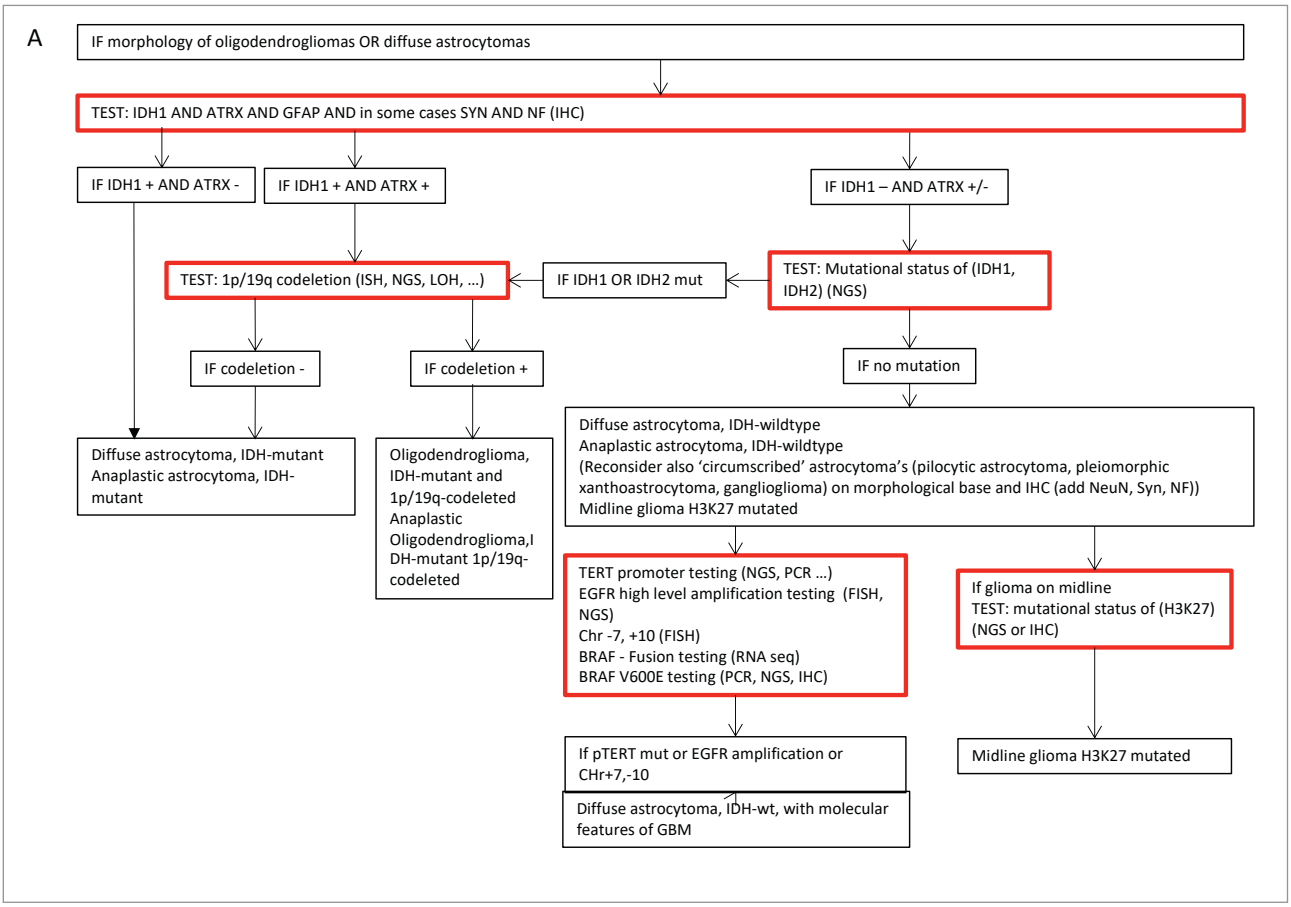
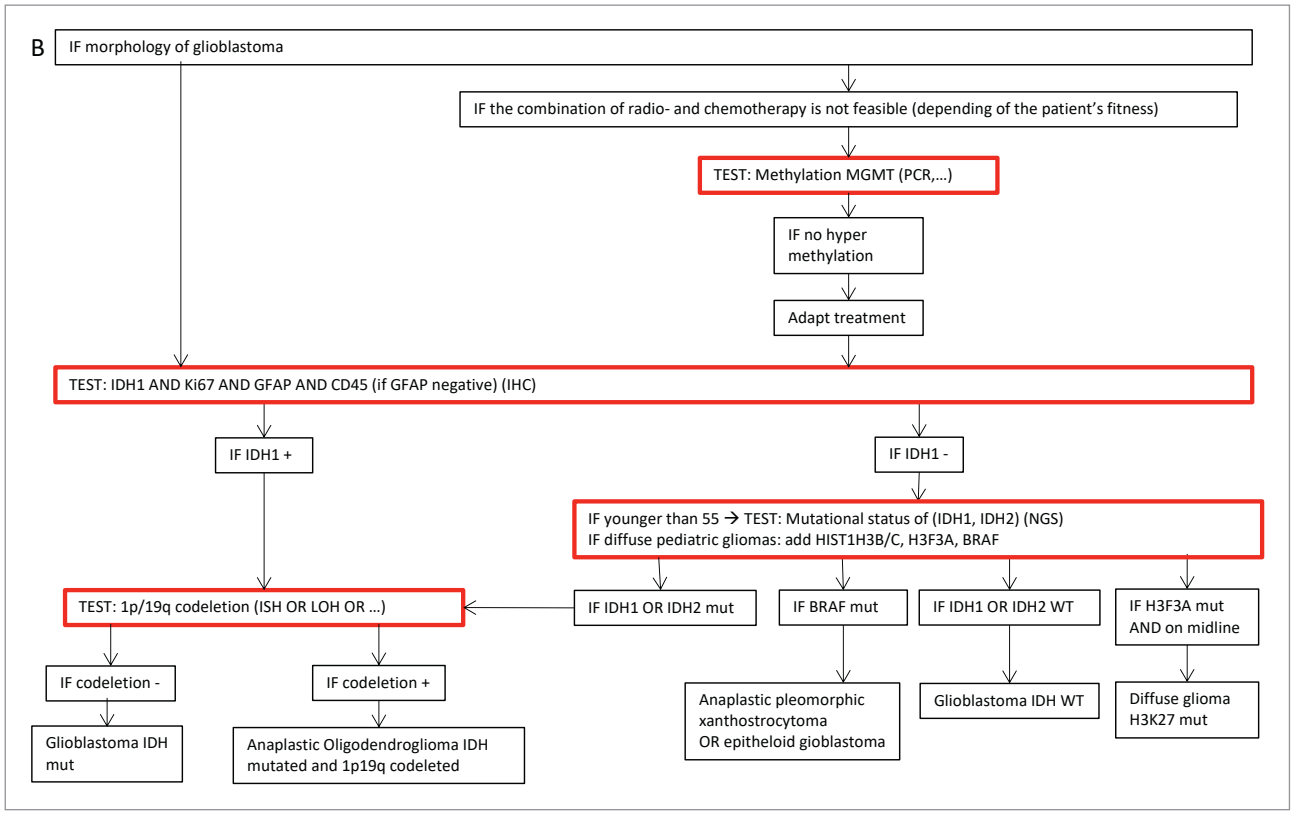


FIGURE 2. Melanoma algorithm.

Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.





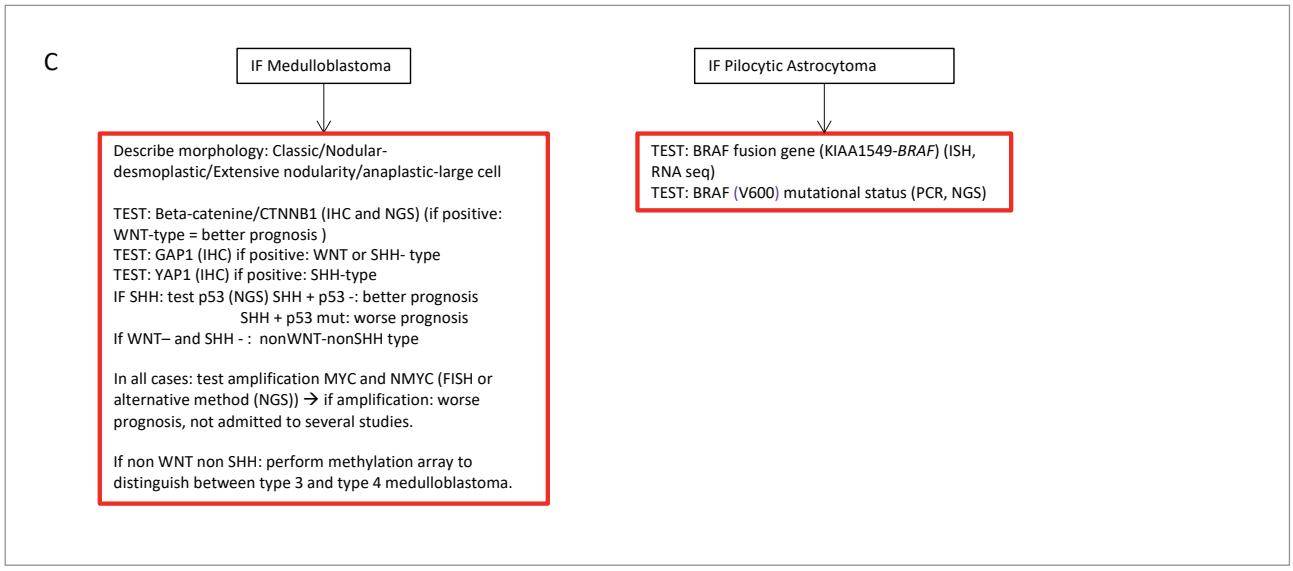


FIGURE 3A-C. Adult brain cancer algorithm.

Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.

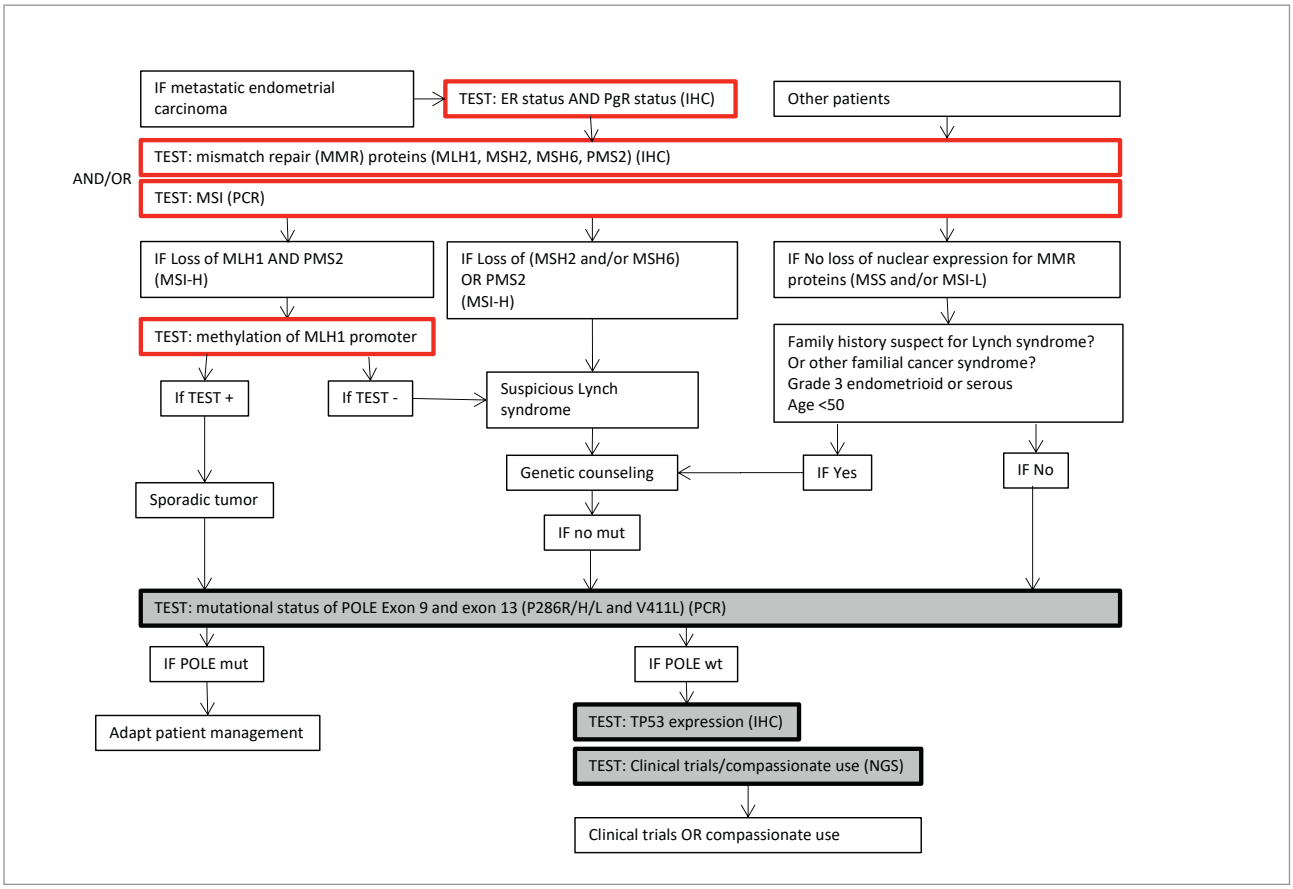


FIGURE 4. Endometrium cancer algorithm.

Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.

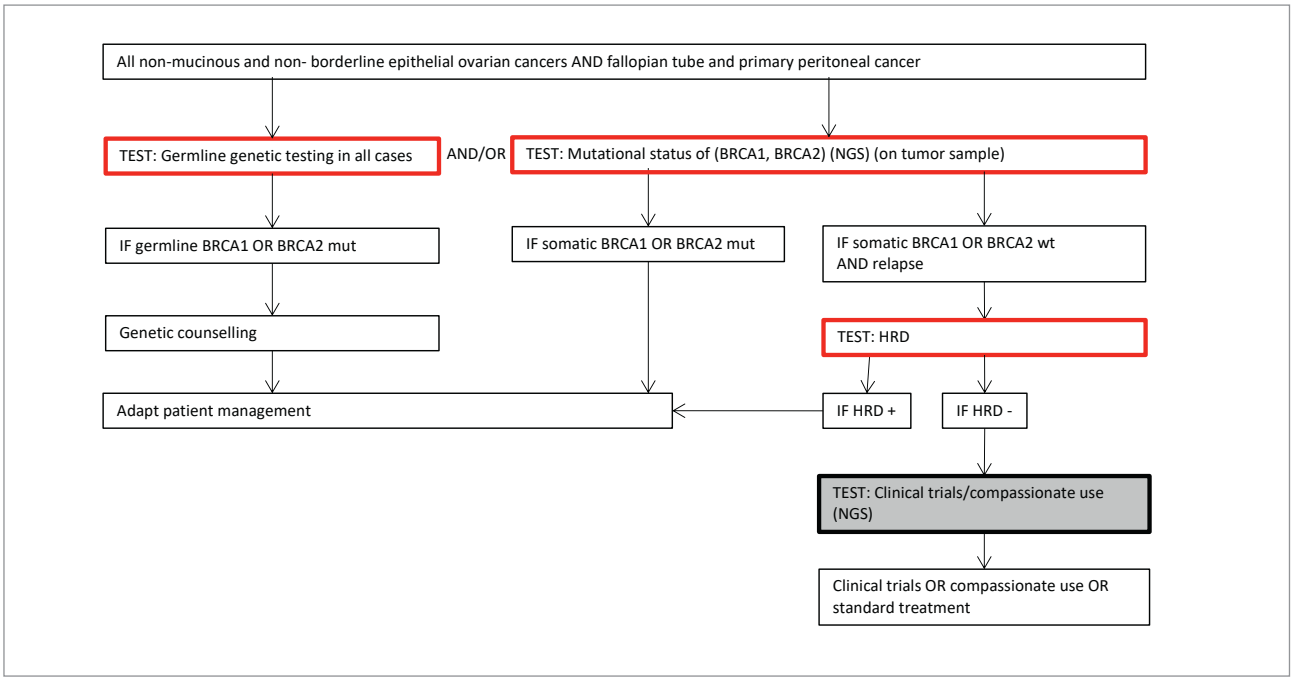


FIGURE 5. Ovarian cancer algorithm.

Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.

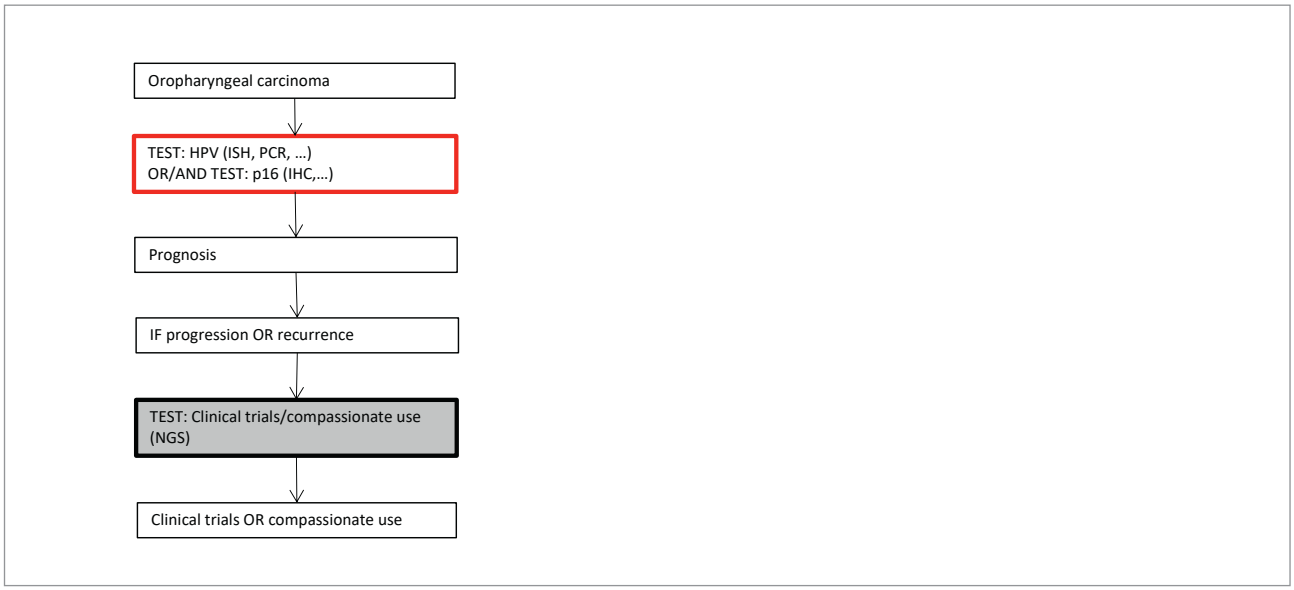


FIGURE 6. Head and neck cancer algorithm.
Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.

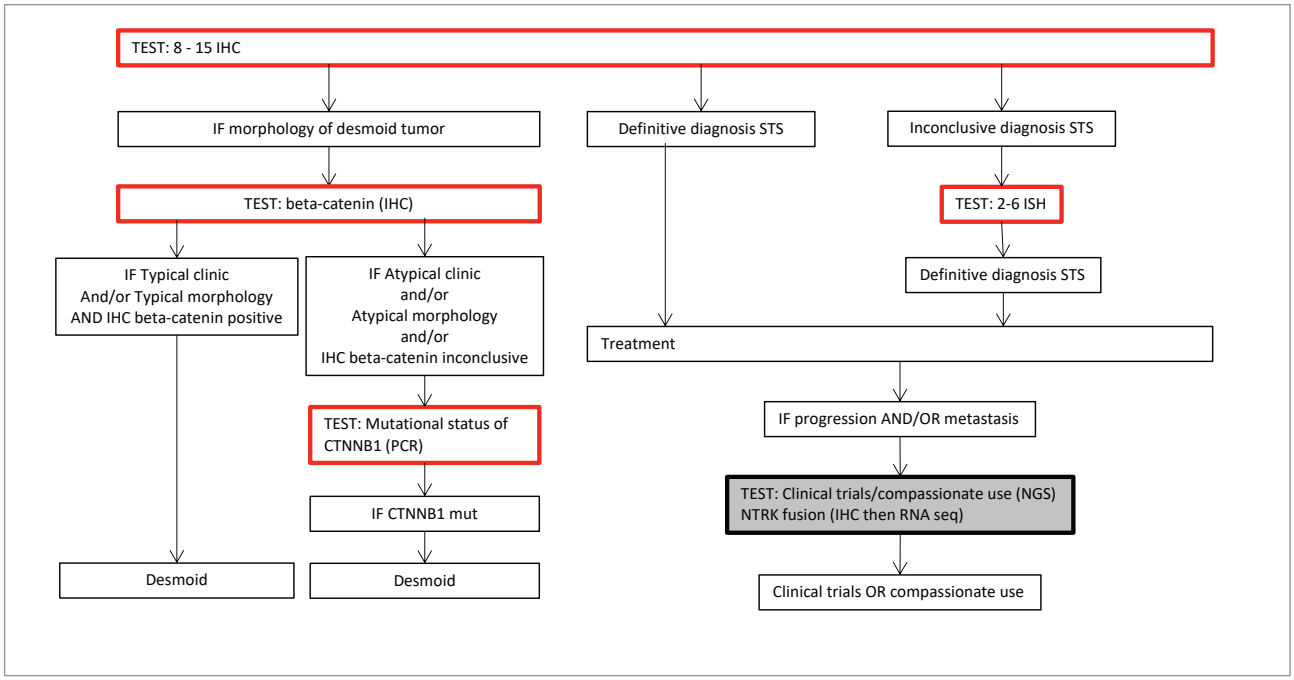


FIGURE 7. Soft tissue tumour algorithm.
Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.

ABBREVIATIONS: *BRAFi: BRAF inhibitor, FISH: Fluorescent In Situ Hybridization, FNA: Fine Needle Aspiration, GBM: Glioblastoma Multiforme, IHC: Immunohistochemistry, ISH: in situ hybridization, LOH: Loss Of Heterozygosity, MEKi: MEK inhibitor, MSI-H: Microsatellite instability - High, MSI-L: Microsatellite instability - Low, MSS: Microsatellite Stable, Mut: Mutated, NGS: Next Generation Sequencing, PCR: Polymerase Chain Reaction, Rearr: Rearrangement, RNA seq: RNA sequencing, SHH: Sonic Hedgehog, STS: Soft Tissue Sarcoma, WT: Wild Type, WNT: Wingless.*

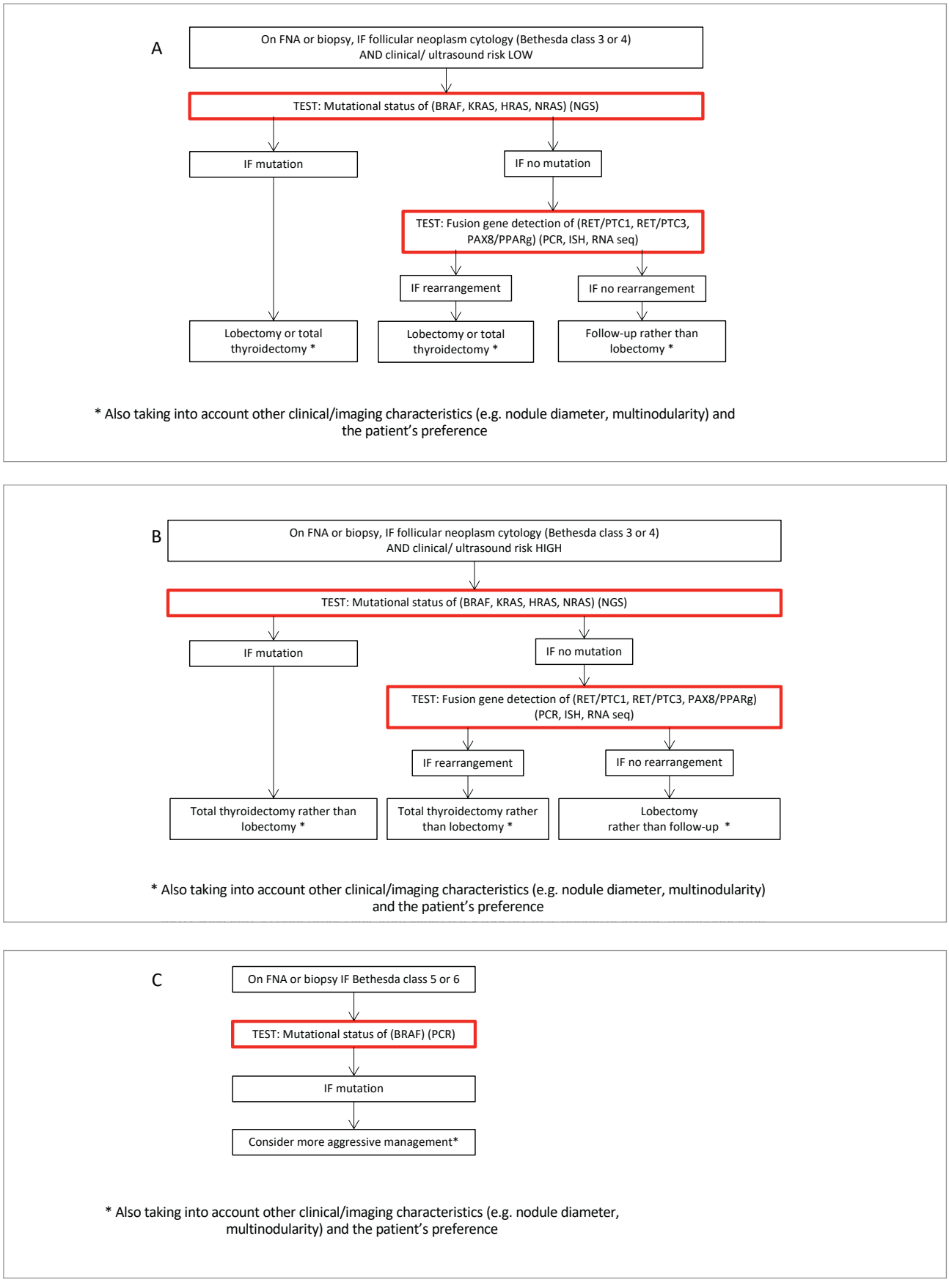


FIGURE 8A-C. Thyroid tumour algorithms.

Molecular tests with level 1 or 2A are represented in a red rectangle, molecular tests with a test level >2A are in a grey rectangle.