

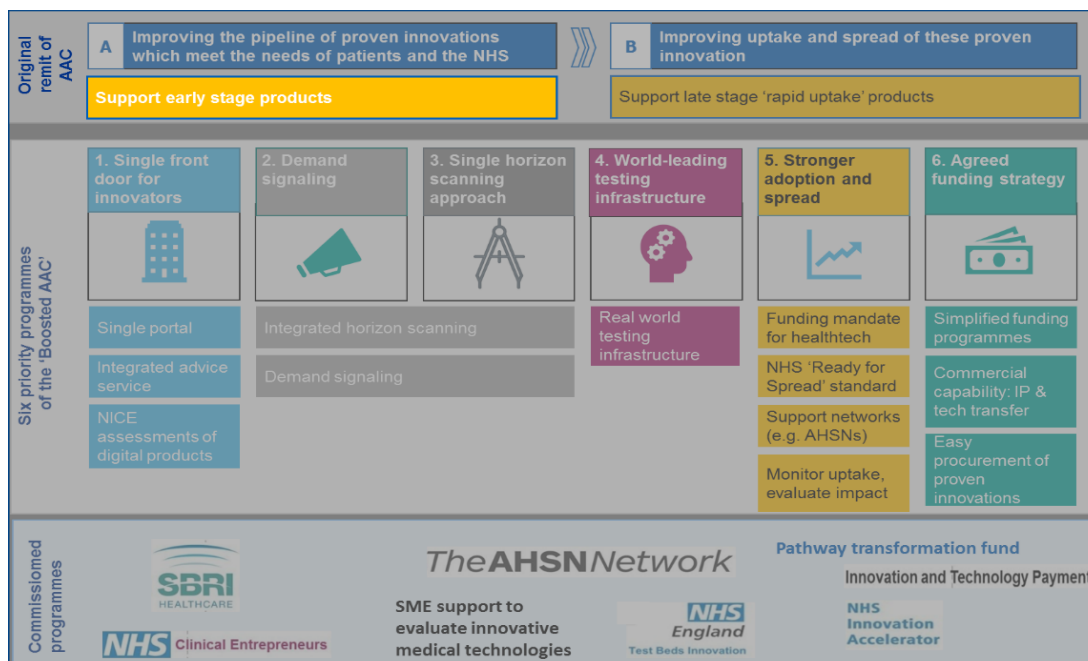
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TUMOUR AGNOSTIC / HISTOLOGY-INDEPENDENT PRODUCTS

Executive summary

1. The AAC Board agreed to prioritise tumour-agnostic products for early stage support at the June meeting.
2. Feedback from key partners suggests that a more appropriate nomenclature for these products, which better aligns across regulatory partners, is 'histology-independent' (HI). Going forward, this terminology will be used within the AAC.
3. HI products represent an opportunity for the NHS to pioneer a new class of cancer therapy, both in terms of diagnostic provision and the robust translation of genomic provision into clinical practice. This paper updates the AAC board on work to support the accelerated access of HI products in the NHS.
4. The paper identifies the main challenges in introducing HI products to the NHS, along with work underway to address them. The challenges can be themed as follows:
 - Implementation planning, including the diagnostic pathway
 - Assessing the value of HI products
 - The position of HI products in multiple cancer pathways.
5. The paper also outlines the implementation plan for two products soon to undergo NICE's value assessment – entrectinib (Roche) and larotrectinib (Bayer).
6. The AAC board is asked to:
 - Consider whether we have identified the key issues in implementing HI products;
 - Agree the proposed actions to help accelerate assessment and adoption of HI products; and
 - Agree the proposed implementation plan for entrectinib and larotrectinib.

Figure 1: Position of this work within the remit of the AAC



Background

- Histology-independent (HI) medicines denote a potential step change in cancer treatment and play an important role in the continued development of personalised healthcare, challenging existing diagnostic and value assessment frameworks.
- This class of treatment is referred to as histology-independent, or tumour agnostic, because of their indication for a solid tumour expressing a particular genomic alteration, regardless of where in the body the cancer originated. This in turn could have implications for how patients with tumours are diagnosed and treated in the NHS.
- One of the first HI products received EMA marketing authorisation this year, with increasing numbers of tumour-agnostic medicines which target the presence or absence of gene mutations anticipated¹. Each genomic change targeted by HI medicines will require testing in the appropriate patient group, and the need for nationwide genomic testing could therefore increase.
- In part, this has led to the NHS's ambition to perform genomic testing to detect relevant mutations and identify treatment options for cancer patients, rather than performing several genomic tests to detect mutations individually. The required mutations for HI medicines could be included in genomic panel testing for treatments for solid tumours. As this testing is still

¹ EMA approval of larotrectinib, 25 July 2019: <https://www.ema.europa.eu/en/medicines/human/summaries-opinion/vitrakvi>

being established in routine practice, however, it presents challenges to the NHS in terms of patient access to, and determining the costs of, genomic testing for HI. This is further exacerbated by the potential for HI therapies to be approved for funding from the end of 2019.

11. Our current estimates show 125 HI therapies currently in trials, with 11 products covering 17 indications due to be evaluated by NICE (Annex A, figure A1). Six HI products are anticipated for market entry in 2020, with approximately 22 anticipated between 2021-24.
12. The first two products entering NICE's appraisal are entrectinib and larotrectinib, designed for cancers with the neurotrophic receptor tyrosine kinase (NTRK) gene fusion^{2,3}. This mutation is commonly present in some rare cancers and rarely present in common cancers. The first two medicines serve to illustrate the relevant issues.
13. Six existing genetic tests cover the 17 indications due to be evaluated by NICE, with five available via the National Genomic Test Directory (NGTD) and one not currently routinely available through the NHS. For entrectinib and larotrectinib, the NGTD includes NTRK testing for some rare tumours e.g. mammary analogue secretory carcinoma of the salivary gland and the secretory variant of breast cancer. In all other adult solid cancers, NTRK gene fusion testing is not currently required by the NGTD.
14. As genomic testing is required to detect genetic mutations for HI therapies, developing an appropriate diagnosis pathway requires infrastructure and workforce changes to administer and access genomic testing on a pan-tumour and national scale.
15. The 26 June AAC board meeting identified HI medicines as a priority. Since then, four interrelated issues have been identified to support accelerated patient access to HI therapies:
 - Implementation planning, including the diagnostic pathway
 - Assessing the value of HI products
 - The position of HI products in multiple cancer pathways
 - Patient engagement and communication.

² Entrectinib - https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212725s000lbl.pdf

³ Larotrectinib - https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211710s000lbl.pdf

Proposed approach to supporting assessment and launch of HI products

Implementation planning, including the diagnostic pathway

16. Developing an appropriate diagnostic pathway requires expansion of the physical infrastructure and workforce needed to administer genomic testing on a national scale. Any solution may also have wider applications in personalised medicine, beyond HI products.
17. The overarching NHS strategy is to move towards gene panel and whole genome sequencing (WGS) where possible, enabling multiple genes linked to a genetic condition to be examined concurrently. As the number of clinically relevant genetic markers expands, running larger panel testing rather than multiple single gene tests can become more cost-effective.
18. The scale of additional testing could pose a risk to ensuring equitable access to HI products. The genomics programme is working to improve access to large panel and WGS testing for cancer patients as part of commitments outlined in the NHS Long-Term Plan. This programme would need to be accelerated to meet the testing required to support the NHS's ambitions for HI therapy access.
19. It is envisaged that all seven Genomic Laboratory Hubs (GLH) could have the capacity and capability to deliver cancer genomic testing specified in the NGTD for their designated geography. Further work is required to assess the incremental infrastructure and workforce development required to meet this anticipated increased demand and to develop a realistic implementation plan.
20. It is currently anticipated that WGS could be operational by Q2 2020/21 and panel testing potentially available by Q1 2020/21. Uptake of molecular testing across the seven genomic hubs may increase during 2020/21 as genomic pathways are embedded and links are made with the clinical teams. Engagement with industry is important in helping to ensure alignment of expectations regarding the NHS's plans for genomic testing roll-out.
21. **To support the implementation of genomic testing:**
 - NHS England and NHS Improvement will continue work to establish the genomic tests required to enable access to HI products, the extent to which the tests are already included within the NGTD, and potential options for staged implementation

Assessing the value of HI products

22. HI products are typically developed in basket trials which have limitations: they cannot include a comparator arm for all tumour types, have small patient populations per tumour type, and usually use objective response rates as the primary end-point. A limited evidence

base, lack of mature progression-free and overall-survival data, a heterogeneous patient population and probable high technology costs also complicate HI products' value assessment.

23. Clinical trials are unlikely to fully represent how patients would be treated across the NHS, particularly regarding where in the treatment pathway a new medicine is used. Particularly for basket trials, it is difficult to establish the degree to which the clinical effect can be extrapolated to those with tumour sites not included in the trial. This creates uncertainty in whether the correct genomic marker is being used to identify the suitable population.
24. The suitability of the comparator used in the clinical trial is central in NICE's value assessment, along with whether clinical trial data supports the case for displacing current therapies, or whether it would be more appropriate to consider best supportive care.
25. The costs of the companion diagnostic also need to be considered in the value assessment for HI products. Including the total diagnostic testing costs in a therapy's value assessment, as is the established approach in NICE's technology appraisals for cancer drugs which require genomic testing, raises questions about reasonableness and proportionality given that the NHS is in parallel considering how to allocate resources to genomic testing and invest in the genomics infrastructure. Thought is therefore required as to how diagnostic costs are proportioned in any cost-effectiveness assessment and whether additional investment in these services may be required for 'pump priming' the new genomics infrastructure.
26. **To support value assessment for HI products the proposal is to:**
 - Work with NICE to ensure the value assessment accounts for changes to treatment pathways and the appropriate proportion of the cost of the diagnostic pathway
 - Include the implications of HI products in the NICE methods review
 - Develop evidence generation for HI products to help manage uncertainty in the diagnostic and treatment pathways.

The position of HI products in multiple cancer pathways

27. There is no single 'typical' treatment pathway for HI products, which can be used across multiple existing pathways.
28. Pathway mapping is complicated by the rare nature of the tumours typically treated by HI therapies, as clinical guidelines may not always be available. As current clinical trials only address a subset of potential patients, it can be difficult to place HI therapies in the treatment pathway. HI products could also potentially be used at different treatment stages depending

on the tumour involved and the number of current standard therapies. There is also the potential for different clinical and cost-effectiveness outcomes across different cancers for the same treatment.

29. The multiple treatment pathway approach may cut across existing NICE guidance processes. This may mean that multiple guidelines require updating each time an HI therapy is approved to prevent contradictions between new HI treatments and current guidance.

30. To ensure effective inclusion of NICE-approved HI products in multiple cancer pathways the proposal is to:

- Develop specialised cancer clinical commissioning expertise on pathway change, in partnership with stakeholders including clinicians and patient groups.
- Work across NHS England and NHS Improvement and NICE to assess implications for existing NICE guidance.

Patient involvement and communication

31. The introduction of HI products into routine NHS use will be challenging and patients and the public need to be able to contribute to discussions on how introduction is managed. We want to hear views on whether our approach to implementation may have a specific impact on different groups of patients. Work on the pathway changes that will result from the introduction of HI products (as described in the section above) also needs to be informed by engagement with relevant patient groups.

32. To ensure our work on HI products is informed by patient views, the proposal is to:

- Work with the national cancer programme, specialised cancer programme of care and genomics programme to identify the most appropriate patient groups
- Define key topic areas and begin targeted engagement
- Ensure that patient groups are appropriately included in the oversight and governance mechanisms for HI product introduction.

Implementation plan for entrectinib and larotrectinib

33. Entrectinib and larotrectinib are to be reviewed by NICE's technology appraisal committee on 20 November 2019. Using approximate timeframes as outline by NICE, and assuming no appeals are received, the earliest these products could be issued with final guidance is late-January 2020.⁴ If the November appraisal committee recommend sending the draft guidance for comments, these timelines could be pushed back to early April 2020.

⁴ NICE technology appraisal approximate timeframes <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/process/sta-timeline>

34. If these products are approved by NICE in January, we would need to have plans in place for testing during January 2020. The average number of patients tested to identify one NTRK variant is around 200. Single gene testing is therefore unlikely to be cost-effective – and panel testing will be required.

35. Over the longer term, the ambition is to introduce panel testing for all cancers. In the short term, we would therefore need to have a staged approach, first focusing on patients with rare tumours who are already eligible to receive NTRK testing, according to the NGTD. One option would be to extend NTRK testing to eligible patients who already receiving panel testing as part of their tumour diagnosis, with the next implementation stage looking to extend NTRK testing to all rare tumours as we introduce panel testing more widely for cancers.

Conclusion

36. Given the increasing attention HI products are receiving from industry, NICE and the NHS, we propose:

- Planning for the implementation of HI therapies, and in particular the diagnostic testing;
- Working with NICE to develop the approach to value assessment, including the impact of changes to the diagnostic and treatment pathways, and handling of the costs of genomic testing and screening; and
- Progressing the cancer pathway for HI products.

37. We also look to further our understanding of the HI pipeline and the next products likely to be approaching NICE for evaluation. This horizon scanning will help prepare the NHS for wider roll-out of TA therapies and inform longer-term planning and strategy.

38. Consideration is also being given to late-stage support for products were previously in the early stage category. This consideration can be found within paper 8 (AAC Support for Late Stage Products).

39. **The AAC board is asked to:**

- **Consider whether we have identified the key issues in implementing HI products;**
- **Agree the proposed actions to help accelerate assessment and adoption of HI products; and**
- **Agree the proposed implementation plan for entrectinib and larotrectinib.**

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ANNEX 1: HI horizon scanning

Information correct at time of publication - information presented is subject to a continually changing clinical landscape.

Figure A1: Pipeline of histology independent products, by phase of development

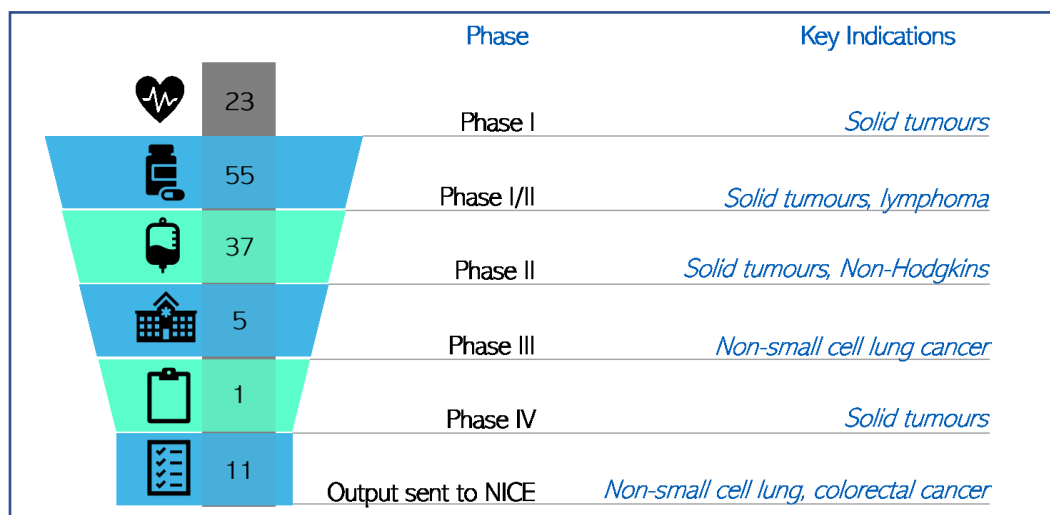


Table A2: Anticipated product timeline to market

Timeline to market	2019	2020	2021	2022	2023	2024
Anticipated number of products (based on analysis in SPS)	2	6				
Anticipated number of products (based on assumptions)	-	~22				

Table A3: HI product volume and indication overview

Unique Companies	69
Number of Products	142
Number of Therapy Areas	20
Key indications	Solid Tumours (98 products)