Contents

What is the purpose of this guide?

This guidance document outlines best practices for establishing standards around the measurement, reporting, and timely communication of insulin and C-peptide test results, particularly in cases where high blood insulin levels are detected in the presence of low C-peptide.

The guide specifically addresses:

- Clinical information required and logistical handling of insulin test requests.
- Requirements for appropriate interpretation and clinical liaison.
- All stages of the diagnostic pathway: pre-analytical (sample collection to lab receipt), analytical (testing process), and post-analytical (result delivery and communication).
- The critical identification and communication of red flag scenarios where hypoglycaemia occurs with elevated insulin but low C-peptide levels.

Who should read this guide?

This guidance is designed for healthcare professionals involved in carrying out insulin testing in adults and children and the investigation of hypoglycaemia (particularly those involved in investigating unexplained hypoglycaemia where rapid identification and communication of clinically significant results can be critical for patient care). As such this includes:

- NHS trusts
- Clinical Biochemists / Chemical Pathologists / Biomedical Scientists working in clinical biochemistry laboratories and key leaders working in clinical biochemistry laboratories
- Endocrinologists, Paediatricians, Neonatologists and other clinicians involved in requesting and interpreting insulin tests
- Clinical Directors
- Medical Directors
- Pharmacists

This document sits alongside the GIRFT and NHS England guide to safe insulin use which focuses on how insulin is safely stored, accessed, prescribed and administered by neonatal services.

Click here to access the guide to safe insulin use.

Introduction

There is currently a lack of standardisation across the country in terms of the measurement, reporting and communication of serum insulin and C-peptide test results for patients of all ages. There is evidence that it is not widely understood by clinicians that there is variation in how insulin is measured, reported and communicated, and that not all laboratories routinely measure insulin and C-peptide, to support distinguishing between endogenous and exogenous insulin sources.

This document will focus on insulin measurement in the context of hypoglycaemia and the role of the laboratory team, including laboratory Clinical Biochemists, Chemical Pathologists, and Biomedical Scientists, and the patient's clinician, in requesting, interpreting, reporting and communicating results to clinicians in these circumstances. Clinical management and investigation of hypoglycaemia and congenital hyperinsulinism is covered in other national resources (see below for further information).

If there is unexplained hypoglycaemia, a glucose, insulin and C-peptide test should be requested, with a rapid turnaround of results.

A robust process must be put in place for the requesting, analysing, reporting, and interpretation of the result with timely clinical liaison when required.

The presence of hypoglycaemia with inappropriately increased insulin and low C-peptide is a red flag scenario and the laboratory must ensure that the relevant medical consultants are informed immediately.

Recommendations

Implementing the following recommendations will help support improving outcomes for insulin testing and the investigation of hypoglycaemia:

Key recommendation

1 Mechanisms must be put in place to ensure that the red flag scenario of hypoglycaemia, elevated insulin and low C-peptide can be rapidly and readily identified.

Pre-analytical

2 **Reason for request:** All tests should be requested within a clinical context, as the exact test(s) required and subsequent interpretation are linked to the reason for request.

All insulin requests must have the reason for request documented so that the receiving and referral laboratories are aware.

3 **Clinical urgency of request:** Linked to the reason for request is the understanding of its urgency; an urgent clinical requirement may require fast-tracking of the sample rather than routine analysis, which could take several days if insulin is batched for analysis locally or sent to a referral laboratory.

Clinicians should clearly articulate the urgency of the request with reasons if urgent analysis is required. Urgent requests should be processed and reported within 48 hours of receipt wherever possible. The exact logistical process should be managed locally, but a mechanism must be put in place to understand the urgency of the request, which will determine the subsequent laboratory handing of the request.

4 **Glucose result:** knowledge of the glucose result is critical in the interpretation of the insulin result.

Glucose must be measured when insulin is requested and, if the insulin is referred to another laboratory, the glucose result must be documented with the reason for the request. If no glucose has been taken, then add on a glucose measurement to an appropriate sample if timing of sample clear or add the comment "*Unable to interpret insulin as no corresponding laboratory glucose measured at the same time.*"

5 **C-peptide:** Interpretation of insulin and glucose requires knowledge of the C-peptide.

Where insulin is requested in hypoglycaemia, a C-peptide request must be included on a sample at the same time (ideally the same sample). Where this has

not been requested by the referring clinician, this should be added by a suitably competent member of the laboratory team.

Analytical

6 **Assay characteristics:** The laboratory receiving the insulin request needs to know what analogues of insulin the assay can detect.

The local laboratory must embed clearly within the standard operating procedure for insulin what the insulin assay can detect and cannot detect. This would refer to both the assay, if done locally, and the method used by the referral laboratory. Local arrangements must be in place so that users and laboratory staff are aware of the assay characteristics. Local laboratories should discuss with their clinicians whether a comment should be added such as "*If the patient is receiving or is suspected to have received exogenous insulin, please contact the lab for interpretation.*"

7 **Variation between assays:** There are a variety of insulin assays, and many have different characteristics. Immunoassays may have variable cross-reactivity with different analogues, different reference intervals, different units of measurement, different lower limit of detection etc. In addition, some laboratories offer methods based on Tandem Mass Spectrometry which may be advantageous but could add to the variation between assays. This could lead to unwarranted variation and confusion. All laboratories offering an Insulin and C-peptide service must be able to advise on what the specificity of the assays are, including what preparations can be, and cannot be, detected.

Insulin assays offered locally would have the characteristics noted locally (see recommendation 6). If there is analytical doubt or interpretative doubt, the telephone number of the reference laboratory should be made available if further advanced discussion is required.

8 To reduce potential confusion with unwarranted variation in reporting units there must be harmonisation of units of measurement to pmol/L.

9 The method used must be attached to the result as a comment.

10 Reference intervals for insulin in the interpretation of insulin and C-peptide levels in the presence of hypoglycaemia are not useful and irrelevant and should either not be reported or to include a relevant comment about the reference interval. However, laboratories providing an insulin and C-peptide service in the investigation of hypoglycaemia should provide guidance and interpretation in hypoglycaemic states.

11 During the discussions on this topic, it became clear that there is unwarranted variation in the methodology used, standardisation, sensitivity, and cross-reactivity of insulin assays in England. It is recommended that External Quality Assurance provide an analytical and interpretative assessment which includes an assessment of insulin assay cross-reactivity.

Post-analytical

12 **Interpretation of insulin results:** Interpretation of insulin results may be critical for patient care.

All referring laboratories, and all referral laboratories should ideally have systems in place for electronic receipt of result in order to speed up the post analytical phase and that the result is therefore received promptly. In laboratories without electronic links, a mechanism must be put in place for the telephoning of clinically significant results in a patient with unexplained hypoglycaemia to the referring laboratory and for these results to be added to the LIMS within 2 hours of receipt of the result.

13 **Clinically significant results:** Clinically significant or unexplained result may have a profound effect on patient care.

Qualified and competent clinical biochemists or chemical pathologists should review the insulin results in line with local protocol, whether performed locally or sent to a reference laboratory. Auto validation of local or referred insulin should not occur. Local protocols should be introduced to ensure that there are no delays in transmission of results to a ward clinicians. If the results are equivocal or interpretation is unclear then experts at a national specialist laboratory should be contacted for advice.

14 **Result display in LIMS and EPR:** Clinically significant results and interpretation must be clearly identifiable in the patient electronic record or LIMS.

All unexplained results must be phoned urgently to a consultant who has responsibility for the patient. This must be recorded within the LIMS, recording the date and time of the call and the person receiving the call. The laboratory has a duty of care to understand that the receiver of the results understands the context of the call and the result. Hypoglycaemia with elevated insulin but low C-peptide levels is a red flag scenario and must be communicated to the requesting clinician, or their team.

15 The electronic record must highlight clinically significant or unexplained results, the interpretation and the offer of further discussion if required.

16 If subsequent retesting is required then the sample should be stored frozen at a minimum of -20°C.

Quality framework

17	A local policy should be written and made available which should include the process from the request, interpretation and communication of results in the investigation of insulin in unexplained hypoglycaemia. This must include the red flag scenario and the urgency of the receipt and communication.
18	All local investigations of hypoglycaemia policies must include information of sample integrity, such as degrees of haemolysis, transport time and conditions of getting sample to the laboratory.

Conclusion

The GIRFT Pathology national report makes it very clear that pathology is much more than a technical service and that qualified and competent clinical staff are required to deliver a clinical interpretative and advisory service as well as clinical leadership of the service provided. There is also a requirement for laboratories to provide clinical interpretation under *ISO15189:2022 Medical laboratories - Requirements for quality and competence*. [4.3a, 5.3.3b, 6.8.2, 7.2.2, 7.2.4.2d, 7.4.1.1a].

This document highlights the role of the laboratory team in the handling and interpretation of insulin requests, especially when investigating the hypoglycaemic patient.

Laboratories should embed these recommendations into routine practice and carry out periodic audits to ensure continued compliance.

It is critical that a process from request to interpretation and communication of results is set up and agreed locally. A local policy should be written and made available.

Further information

Recommended document	Author	Overview
Pathology GIRFT Programme National Specialty Report	GIRFT (2021)	National report for pathology which aims improve the patient experience 'end-to-end' – widening the focus of NHS pathology to look across the entire service, from the point at which a clinician considers a test to the patient's interpretation of the results.
Identification and Management of Neonatal Hypoglycaemia in the Full-Term Infant (Birth – 72 hours)	British Association of Perinatal Medicine (2017, revised 2024)	A framework for practice to address variation in practices in the definition of hypoglycaemia, the identification, management and admission thresholds of babies admitted to neonatal units for hypoglycaemia.
Investigation of hypoglycaemia in infants and children	MetBioNet (2025)	Laboratory guidelines reflecting current best practice in specialist metabolic laboratories the UK.
International Guidelines for the Diagnosis and Management of Hyperinsulinism	Horm Res Paediatr. (2024)	International consensus statement on diagnosis and management of HI was developed in order to assist specialists, general paediatricians, and neonatologists in early recognition and treatment of HI with the ultimate aim of reducing the prevalence of brain injury caused by hypoglycaemia.
Standardised practices in the networked management of congenital hyperinsulinism: a UK national collaborative consensus	Frontiers in Endocrinology (2023)	A UK-wide consensus on managing congenital hyperinsulinism which aims to harmonize CHI management practices across the UK, ensuring timely diagnosis, effective treatment, and comprehensive support for affected individuals and their families.
Diabetes (type 1 and type 2) in children and young people: diagnosis and management	NICE (Published 2015, updated 2023)	NICE guideline which covers the diagnosis and management of type 1 and type 2 diabetes in children and young people aged under 18.
ISO 15189 Medical laboratories. Requirements for quality and competence	UKAS (2023)	The established international standard on quality and competence requirements in medical laboratories.

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About GIRFT and the GIRFT Academy

Getting It Right First Time (GIRFT) is a clinically-led national programme designed to identify and minimise unwarranted variation in treatment and care delivered. It undertakes clinically-led reviews of specialties, combining wide-ranging data analysis with the input and professional knowledge of senior clinicians to examine how things are currently being done and how they could be improved.

The programme has the backing of the Royal Colleges and professional associations and has a significant and growing presence on the Model Health System portal, with its data-rich approach providing the evidence for hospitals to benchmark against expected standards of service and efficiency.

The GIRFT model has now been applied in more than 50 different areas of clinical practice. It consists of five key strands:

1. Data Gathering – a broad data gathering and analysis exercise, generating a detailed picture of current national practice and outcomes.
2. Peer Reviews – direct clinical engagement via visits or virtual meetings between clinical leads and trust teams; an opportunity to examine trust behaviour in the context of the national picture, enabling teams to understand where they are performing well and what they can do better.
3. National Report & Academy resources – production of national reports that draw on data analysis and discussions with provider teams to identify opportunities for improvement, locally, regionally and nationally, alongside - clinical resources such as best practice pathways and guides.
4. Support to deliver – the implementation phase where the GIRFT team supports trusts, commissioners and integrated care systems to deliver the improvements recommended.
5. Research & Development – GIRFT fellowships support resident doctors, nurses and allied health professionals to develop their research and clinical improvement skills, delivering research projects and GIRFT identified improvements in their host provider, system or region.

For the latest version of this document, please see www.gettingitrightfirsttime.co.uk or Getting It Right First Time - FutureNHS Collaboration Platform

GIRFT and a greener NHS

Climate change is one of the greatest health threats and opportunities of the 21st century. The NHS is acting now to mitigate and adapt to this threat in order to protect the health of current and future generations. Doing so will not only protect the environment but will also bring many health, social and financial benefits. As the largest employer in the UK, contributing 4.6% of national emissions, the NHS is both part of the challenge and the solution.

Through its endeavour to improve the quality of care within the NHS by reducing unwarranted variation, GIRFT can play an important role in reducing the carbon emissions associated with care delivery. Through the GIRFT model, there is the opportunity to identify changes that will help reduce the NHS carbon footprint and therefore improve patient care now and in the future.