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Genetic testing date:	10/01/2023		
Blood metal ion testing date:	01/2023	Age at time of primary:	53 Years Old
Report date:		Duration implant in vivo:	7 Years
Patient name:		Device:	Knee implant - Other
Date of birth:	11/01/1963	Blood chromium concentration:	5 µg/l
Gender:	M	Blood cobalt concentration:	5.2 µg/l
NHS number:		Blood titanium concentration:	0.5 µg/l
Date of primary:	2016	Referring doctor:	
Hospital name:			

OrthotypePlus results of genotyping and survival predictions:

Based on this individual's genotype and clinical parameters, Orthotype™ **indicates the presence of an active adverse reaction to metal debris (ARMD)**. There is a 43% risk that this adverse response involves T lymphocyte recruitment (ALVAL/metal hypersensitivity*).

The survival predictions shown in the chart below are generated from an algorithm developed and validated using results from a total cohort of 606 patients[¥] with metal-on-metal total hips or hip resurfacings (manufactured from standard medical grade cobalt chrome alloy).

The comparator curve shows the risk of ALVAL for an age and sex matched patient, with optimal metal ion concentrations (< 2 micrograms per litre) using the common European genotypes for the predictions (with the exclusion of the current patient's genotype).

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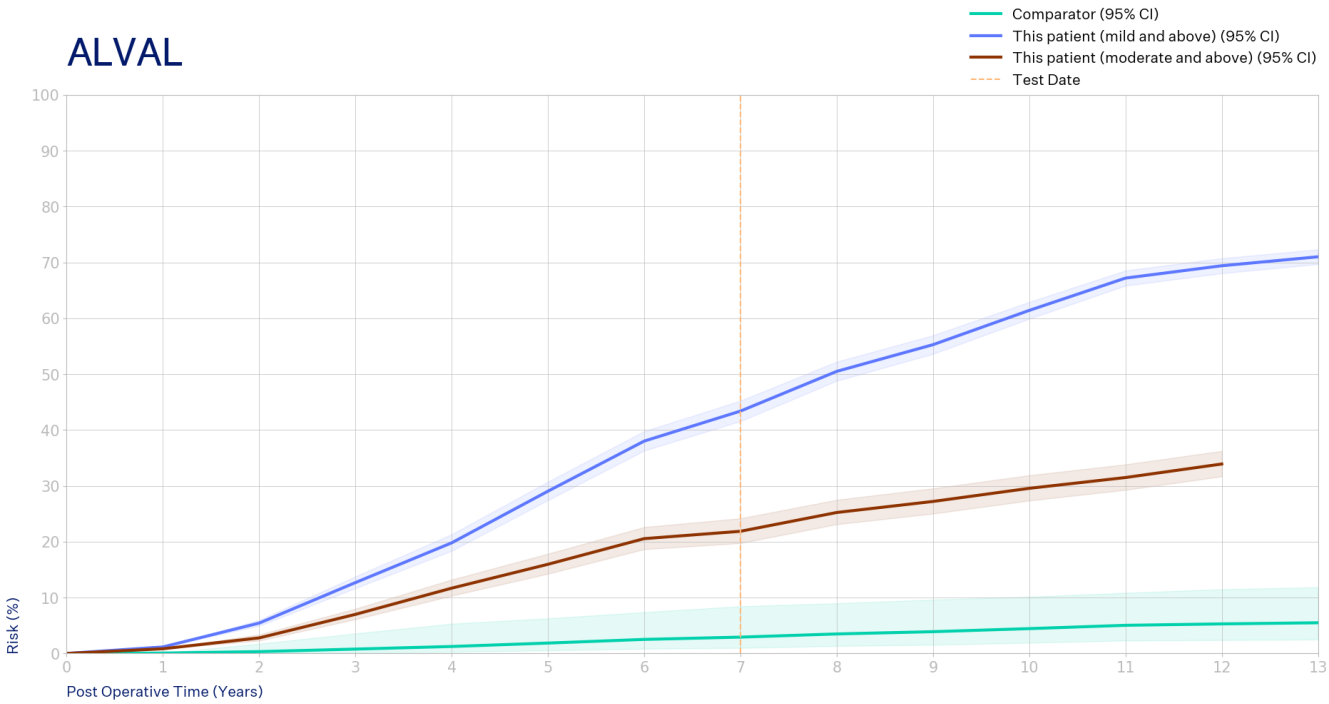
ALVAL



Orthotype indicates presence of active ARMD

Sensitivity = 88.8%, 95% CI [84.0, 93.3]**
Specificity = 89.5%, 95% CI [86.5, 92.3]**

43% risk of ALVAL response for this patient at test date

Risk for the comparator group is 3%

Risk of high grade ALVAL for this patient is 22%

Adverse reaction to metal debris (ARMD) is an umbrella term covering the full spectrum of metal debris related pathology.

ALVAL refers to a specific subset of ARMD, in which there is T lymphocyte recruitment to the periprosthetic tissue and a greater risk of progressive soft tissue damage (delayed type hypersensitivity).

High grade ALVAL indicates synovial membrane necrosis.

See “terminology” section below for greater detail.

⚠ *Predictions for ALVAL, high grade ALVAL, and ARMD have been validated to 13, 12, and 15 years post operative follow up respectively. If the patient has been tested beyond these time points, only the risks at 13, 12, and 15 years are presented.*

⚠ *Patients with bilateral CoCr implants: The survival predictions assume that prostheses are generating approximately equal amounts of CoCr metal debris.*

⚠ *Orthotype™ is intended to be used in the assessment of primary joint replacements in patients with normal renal function.*

**
For positive tests, out of 100 patients testing positive, approximately 11 (11.2%) will not have ARMD (i.e. false positives). For negative tests, out of 100 patients testing negative, approximately 11 (10.5%) will have ARMD (i.e. false negatives).

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The Orthotype™ Test ⚠

Orthotype™ was developed and validated through the study of patients with metal-on-metal total hip or hip resurfacing arthroplasties which were manufactured from standard medical grade cobalt chrome components. The accuracy of the survival predictions for other joint arthroplasties containing cobalt chrome (such as the most commonly used total knee arthroplasties) has not been validated. However, there is no strong evidence to suggest that HLA genes show greater activity in different joints in the body.

Orthotype™ is intended to be used in the assessment of primary joint replacements. If a patient was previously implanted with a CoCr device but now has a new (revision) implant, sensitisation may have occurred to the previous implant, which may have been wearing at a higher rate than the implant currently in situ. In this situation, the current blood Co and Cr concentrations may not provide a reliable indicator of the overall metal debris exposure and the risk of ARMD/ALVAL may be underestimated. In this situation Orthotype™ can be used as a guide for the general, relative risk associated with the patient's genotype, but the survival curves should not be viewed as reliable.

Metal ion concentrations in context ⚠

The development of ARMD depends upon an interaction between patient factors, and the amount of metal exposure over time. Blood or serum metal ion concentrations provide a reliable assessment of metal exposure. For context, well-functioning metal on metal hip bearings wear at less than 1mm³ per year. This level of wear generally equates to blood or serum cobalt concentrations less than 2 micrograms per litre.

¥Genetic diversity in different populations ⚠

The Orthotype™ validation study involved patients who were mostly of European descent, resident in the North East of England (the United Kingdom), New York (United States) and Perth (Australia). Different human populations can display different genetic associations to the same disease processes.

*Terminology

Adverse reaction to metal debris (ARMD) is an umbrella term covering:

- Macrophage responses in association with pain and/or bone and/or soft tissue damage
- "Pseudotumour" formation which may be solid or cystic and accompanied by a mixed histological response
- ALVAL/Delayed type metal hypersensitivity
- Metallosis

Delayed type metal hypersensitivity:

- Delayed type metal hypersensitivity refers to the development of perivascular T cell lymphocytic aggregates in the periprosthetic tissue
- The term is used interchangeably/is synonymous with aseptic lymphocyte dominated vasculitis association lesion (ALVAL)
- The thresholds for "ALVAL/metal hypersensitivity" in this report are defined according to the description by Natu et al (Journal of Clinical Pathology, 2012)
- ALVAL: Formation of perivascular cuffs by T cell lymphocytes (includes "mild", "moderate" or "severe" ALVAL grades)
- High grade ALVAL: Large perivascular lymphocyte aggregates with synovial membrane necrosis +/- development of tertiary lymphoid organs ("moderate" or "severe" ALVAL)

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Titanium concentrations in context

Analysis performed at SAS Trace Element Laboratory, Guildford, using triple quadrupole inductively coupled plasma mass spectrometry.

Note that this is a stand alone laboratory test. It is not used in the Orthotype™ algorithm.

Whole blood titanium concentration = 0.5 micrograms per litre.

Analysis of previously published results from the same laboratory were analysed and compared to clinical results of a group of 124 patients with hip replacements and hip resurfacings. For the patients who subsequently underwent revision, the explanted components were analysed to determine whether there were signs of abnormal wear and/or corrosion at the component surfaces and/or modular interfaces.

Below is a summary of the findings from receiver operative curve analysis:

2ug/l - The upper limit of normal for patients who either have arthroplasties with low wearing titanium implants or arthroplasties with no titanium components.

2 to 3ug/l - The range which may be indicative of abnormal wear processes. Currently, it is unclear which patients may be more or less sensitive to titanium concentrations in this range and who may be at risk of developing adverse clinical sequelae.

Over 3ug/l - Showed 87% (95% CI: 79 – 92) specificity for pain or osteolysis in conjunction with a biomechanical issue (taper junction failure/component loosening/impingement) leading to revision surgery. The equivalent value for sensitivity was 71% (95% CI: 51 – 85). The suggested cut off of 3ug/l is consistent with literature published from other centres.

Over 5ug/l - Showed 97% specificity (95% CI: 91-99) for pain or osteolysis in conjunction with a biomechanical issue (taper junction failure/component loosening/impingement) leading to revision surgery. The sensitivity was 38% (95% CI: 21 – 57).