Kir Genotyping Using Polymerase Chain Reaction (PCR) (Reference – 2013.02.007)

Notice of Assessment

December 2013
1 GENERAL INFORMATION

1.1 Requestor: Hôpital Maisonneuve-Rosemont
1.2 Application Sent to MSSS: June 6, 2011
1.3 Application Received by INESSS: July 1, 2013
1.4 Notice Issued: October 31, 2013

Note:
This notice is based on the scientific and commercial information (submitted by the requestor[s]) and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)

2.1 Name of the Technology
KIR (killer-cell immunoglobulin-like receptor) genotyping by polymerase chain reaction (PCR) with sequence-specific primers (SSP).

2.2 Brief Description of the Technology, and Technical and Clinical Specifications
Currently, two kits are used to perform the test. Each is used to validate the results of the other. However, following validity studies, only one kit will be needed to carry out the test.

One of the kits is KIR Genotyping SSP (Cat. No.: 78930-3), from the Invitrogen company (Life Technologies). It is stored at -20°C and comprises 12 tests. It also includes the PCR buffer. The test sample was already extracted for other tests (HLA typing at loci A, B, C, DRB1 or DQB1). To begin the test, the material is removed from the freezer and allowed to reach room temperature. Using pipettes and sterile nozzles, the reaction mixture is prepared and transferred onto microtitre culture plates. A sealant is applied to the plate prior to amplification with PCR-SSP. The thermocyclers used are Biometra® TProfessional standard (Montréal Biotech, Cat. No.: 070-951) or ABI 9700 (Life Technologies Cat. No.: N8050001). When the amplification is complete, the DNA is run on an agarose gel with ethidium bromide, and the migration pattern is visualized and analyzed to determine which KIRs are present in the subject.

The second kit used for validation is the KIR typing kit (Cat. No.: 130-092-584) by Miltenyi Biotec. The kit comprises 24 tests and is stored at 4 °C. The test procedure is similar to the aforementioned.
2.3 **Company or Developer:** based on the method published by Gómez-Lozano and Vilches (2002).

2.4 **Licence:** Not applicable.

2.5 **Patent, If Any:** Not applicable.

2.6 **Approval Status (Health Canada, FDA)**

According to the requestor, the KIR Genotyping SSP Kit by Invitrogen (Life Technologies) is approved by Health Canada, but a database search of the Medical Devices Active Licence Listing (MDALL) [Health Canada, 2013] failed to locate it.

The KIR typing kit by Miltenyi Biotec was also not found in the MDALL database. The information provided by the manufacturers of the kits indicates that their use is limited to research.

2.7 **Weighted Value:** 111.66. This estimate was calculated in July 2009.

3 **CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES**

3.1 **Targeted Patient Group**

Patients with a hematologic malignancy (leukemia, lymphoma and myeloma) requiring hematopoietic stem cell transplantation, to find a haploidentical donor.

3.2 **Targeted Disease(s)**

Hematologic malignancies are a collection of heterogeneous conditions originating from cells of the bone marrow and the lymphatic system [Rodriguez-Abreu et al., 2007]. The three major groups are: leukemia (including acute and chronic myeloid leukemia, acute lymphoblastic leukemia, and B-cell chronic lymphocytic leukemia), lymphoma (Hodgkin and non-Hodgkin lymphoma), and plasma cell neoplasms (multiple myeloma). The prognosis depends on the type of hematologic cancer. Regarding incidence and mortality in Canada, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia and multiple myeloma together have accounted for 9.12% \((n = 17,110)\) of all new cancers between 2003 and 2007; three of these conditions (with the exception of Hodgkin lymphoma) represent 9.14% \((n = 6,897)\) of all cancer-related deaths during the same period [CCSCC, 2013]. Extrapolated to Quebec's population, the data suggest 855 new cases and 345 deaths per year. The incidence of different types of hematologic cancer varies with age. Leukemia, in particular, is a leading cause of cancer death in individuals under 30 years of age (27% of cancer deaths in individuals aged 0 years to 14 years, and 17% of cancer deaths in individuals aged 15 years to 29 years) [CCSCC, 2013].

3.3 **Number of Patients Targeted**

The requestor estimates the number of tests at approximately 48 per year over the next 3 years for Quebec.

According to the requestor, it is technically feasible for other establishments to perform this test if it is included in the Index. The technique is easy to implement in laboratories that already conduct PCR. However, the interpretation of the results is very complex.

Moreover, from a regulatory standpoint, laboratories performing HLA typing must be accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), as is the laboratory of the Hôpital Maisonneuve-Rosemont (HMR). Likewise, KIR genotyping should be performed in ASHI-accredited laboratories to ensure that quality standards are met. For the time being, HMR is the only transplant centre designated to offer this type of test. Patient eligibility for this testing will be determined by the patient’s doctor. HMR laboratories will offer this test to all doctors and establishments requiring it.
3.4 Medical Specialties Involved
Hematology/oncology, genetics.

3.5 Testing Procedure
Blood samples are obtained from the patient and from the potential donor by venipuncture at the hospital.

4 TECHNOLOGY BACKGROUND

4.1 Nature of the Diagnostic Technology: Unique.

4.2 Brief Description of the Current Technological Context
Half of the patients with hematologic malignancies who require adoptive immunotherapy\(^\text{13}\) have been unable to benefit from allogeneic hematopoietic transplantation due to the challenges and delays inherent in the identification of compatible donors, donor HLA typing, bone marrow harvest, etc. [Velardi, 2008]. In the past, stem cell transplantations from HLA-mismatched donors often led to high incidence of complications, such as graft-versus-host disease (GVHD) and transplant rejection [Fuchs, 2012; Reisner et al., 2011; Velardi, 2008].

4.3 Brief Description of the Advantages Cited for the New Technology
KIR typing increases the number of potential donors, as it enables the selection of haploidentical donors (e.g., a 5/10 or greater HLA-matched donor compared with a 10/10 HLA-matched identical donor). The principle of natural killer (NK) cell alloreactivity (donor-versus-recipient) involves an NK cell subpopulation in a donor. These cells express inhibitory receptors (KIRs) that do not recognize HLA class I ligands (HLA-I) on the recipient's tumour cells and function as mediators of alloreactions [Velardi, 2008; Nguyen, 2007]. Thus, this method leads to fewer GVHD complications [Negrin, 2013; Reisner et al., 2011; Olson et al., 2010].

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\(^\text{13}\) Adoptive immunotherapy: a method that involves stimulating anticancer cells outside the patient's body \textit{(in vitro)} and then reinjecting them into the patient's body [Termium, 2012] Available at: http://www.btb.termiumplus.gc.ca/tpv2alpha/alpha-fra.html?lang=fra&i=&index=alt&__index=alt&srchtxt=adoptive+immunotherapy&comencsrch=x=9&comencsrch.y=1.
4.4 Cost of Technology and Options

Based on the information provided by the requestor, the weighted value of the test was estimated at 111.66 in 2009. The requestor's laboratory is already supplied with all the equipment needed to perform this test.

5 EVIDENCE

5.1 Clinical Relevance

5.1.1 Other Tests Replaced

This new test does not replace an existing test.

5.1.2 Diagnostic or Prognostic Value

The study conducted by Kanga et al. [2012] assessed the effect of donor KIRs and recipient HLA ligands on the results of sibling hematopoietic stem cell transplantation. The study included 26 patients with various hematologic malignancies who had received peripheral blood stem cell transplantation from related donors. The patients were monitored for 4.5 years, and the rate of GVHD, relapse and overall survival were assessed. The absence of ligands was observed in 88.5% of cases. Among mismatched cases, 39% of the subjects developed GVHD. The presence of C1, C2 and the Bw4-80(T) allele showed a protective effect against GVHD. The authors concluded that the role of KIRs may depend mainly on the type of transplantation and the conditioning regimen.

The study by Ruggeri et al. [2007] analyzed 112 patients with high-risk acute myeloid leukemia who received HLA-haploidentical transplants from NK alloreactive (n = 51) or non-NK alloreactive donors (n = 61). Transplantation from NK-alloreactive donors was associated with a significantly lower relapse rate in patients in complete remission (3% versus 47%, P > 0.003), better event-free survival in patients post-transplant after 10 years of follow-up, a lower relapse rate (34% versus 6%, P = 0.04) and reduced risk of relapse or death RR 0.48 (95% CI, 0.29 to 0.78; P > 0.001). The authors concluded that only transplantation from NK-alloreactive donors is associated with a survival advantage.

Elmaagacli et al. [2005] examined how KIR ligand incompatibilities caused relapse in 236 patients with chronic myeloid leukemia. The recurrence, GVHD, mortality, overall survival, event-free survival and primary graft failure rates were assessed in three groups who had received hematopoietic stem cell transplantations (HLA-identical [Group 1: n = 158], HLA class I antigen mismatched and KIR-ligand compatible [Group 2: n = 49], and HLA class I antigen mismatched and KIR-ligand incompatible [Group 3: n = 29]). Molecular relapse in groups 1, 2, and 3 was 39%, 22% and 3%, respectively (P < 0.001). Hematologic relapse in groups 1, 2, and 3 was 13%, 4% and 0%, respectively (P < 0.05). The incidence of acute GVHD was lower in groups having received an HLA-identical graft (P < 0.05), but the incidence of chronic GVHD was similar in the three groups. There was no significant difference between the groups in terms of graft failure or survival. Although the author used KIR genotyping, the methodology used was real-time reverse-transcription PCR and chimeric analysis, not PCR-SSP.

Various clinical studies have reported some success with HLA-mismatched/haploidentical blood or bone marrow transplantation in patients with hematologic malignancies [Bashey et al., 2013; Di Bartolomeo et al., 2013; Guo et al., 2012; Brunstein et al., 2011; Lu et al., 2006], but these studies do not specify whether KIR genotyping was used to select the donors.

5.1.3 Therapeutic Value

KIR genotyping would increase the number of potential donors and allow the option of transplantation in cases where an identical match is not possible.
5.2 **Clinical Validity:** No studies of the clinical validity of KIR typing were identified.

5.3 **Analytical (or Technical) Validity**

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Only one study of analytical validity [Abalos et al., 2010] compared ten DNA reference samples from KIR genotyping obtained from healthy donors from the National Cancer Institute (United States). The results from these samples were obtained using the KIR Genotyping SSP Kit and KIR genotyping by PCR-SSP, as proposed by the authors. A 100% concordance was observed among the three genotyping methods.

5.4 **Recommendations for Listing in Other Jurisdictions**

The clinical practice guidelines reviewed do not address the issue of KIR genotyping in hematologic cancers.

6 **ANTICIPATED OUTCOMES OF INTRODUCING THE TEST**

6.1 **Impact on Material and Human Resources:** Not assessed.

6.2 **Economic Consequences of Introducing the Test Into Quebec's Health Care and Social Services System:** Not assessed.

6.3 **Main Organizational, Ethical, and Other (Social, Legal, Political) Issues**

The stem cells for these transplants are generally obtained from bone marrow or by apheresis. Some studies have also used umbilical cord blood [Brunstein et al., 2011; Reisner et al., 2011].
7 IN BRIEF

7.1 Clinical Relevance
Allows patients who cannot find a compatible donor to receive stem cell treatment.

7.2 Clinical Validity
No clinical study has used this particular typing technique, but limited data suggest that it may be relatively effective.

7.3 Analytical Validity
Very limited data suggest good concordance with other KIR genotyping methods.

7.4 Recommendations for Listing in Other Jurisdictions
There were no clinical guidelines available on the use of KIR typing in cases of hematologic malignancy.
8 INESSS NOTICE IN BRIEF

KIR (killer-Cell Immunoglobulin-Like Receptor) Genotyping Using Polymerase Chain Reaction (PCR)

Status of the Diagnostic Technology

☐ Established
☒ Innovative
☐ Experimental (for research purposes only)
☐ Replacement for technology: _______________________, which becomes obsolete

INESSS Recommendation

☐ Add test to the Index
☐ Do not add test to the Index
☒ Reassess test

This test can save lives.
The requestor’s establishment is the only one in Canada that performs this test.
Clinical validity data are necessary to complete the assessment.
A reassessment will be done when the requestor has provided data on the results obtained in the requestor’s laboratory.

Additional Recommendation

☐ Draw connection with listing of drugs, if companion test
☐ Production of an optimal use guide
☐ Production of indicators, when monitoring is required
REFERENCES


