PIRCHE Matching Service

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GIORNATA DI FORMAZIONE AIBT

TOOLS BIOINFORMATICI E RISORSE WEB IN ISTOCOMPATIBILITA’

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PIRCHE è il nome di una nuova tecnologia basata sull’uso di algoritmi informatici che consentono di stimare il rischio della risposta immune dopo il trapianto

1. Trapianti di organi solidi (SOT):
   Predittivo dello sviluppo di de novo anticorpi donatore specifici (DSA)
   Consente di identificare i trapianti ad alto rischio

2. Trapianto di cellule staminali ematopoietiche (HSCT):
   Predittivo del rischio di sviluppo di GVHD
   Consente di selezionare il donatore con il mismatch più permissivo

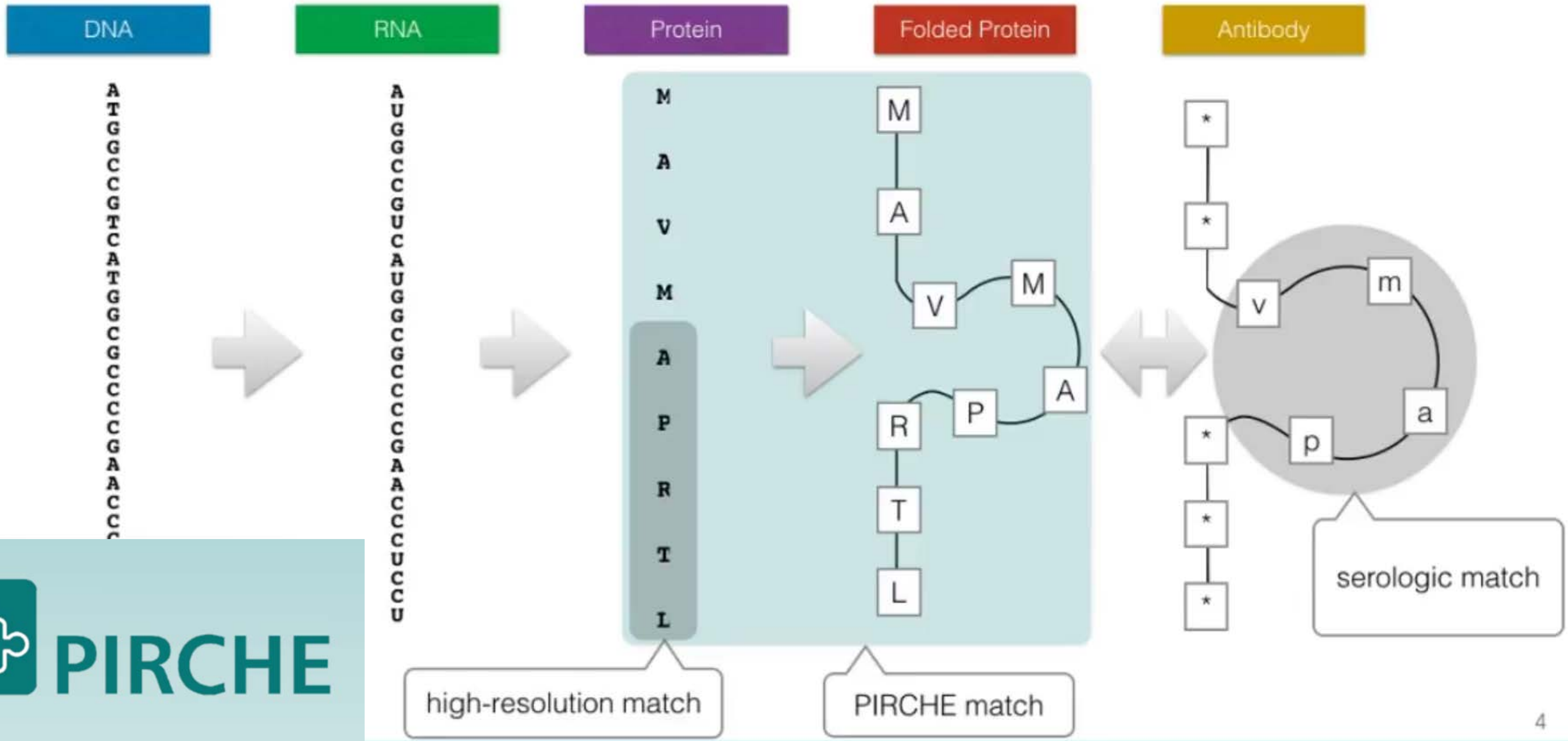
PIRCHE

PIRCHE = Predicted Indirectly ReCognized HLA derived T cell Epitopes

- Sviluppato da Eric Spierings, University Medical Centre Utrecht
- Valuta il livello di matching HLA tra donatore e ricevente prevedendo gli epitopi HLA riconosciuti con modalità indiretta dai linfociti T
- Considera le proprietà di legame delle molecole HLA con il peptide
- Tipizzazione HLA del donatore e del ricevente

PIRCHE

Matching Strategies



DNA

RNA

Protein

Folded Protein

Antibody

high-resolution match

PIRCHE match

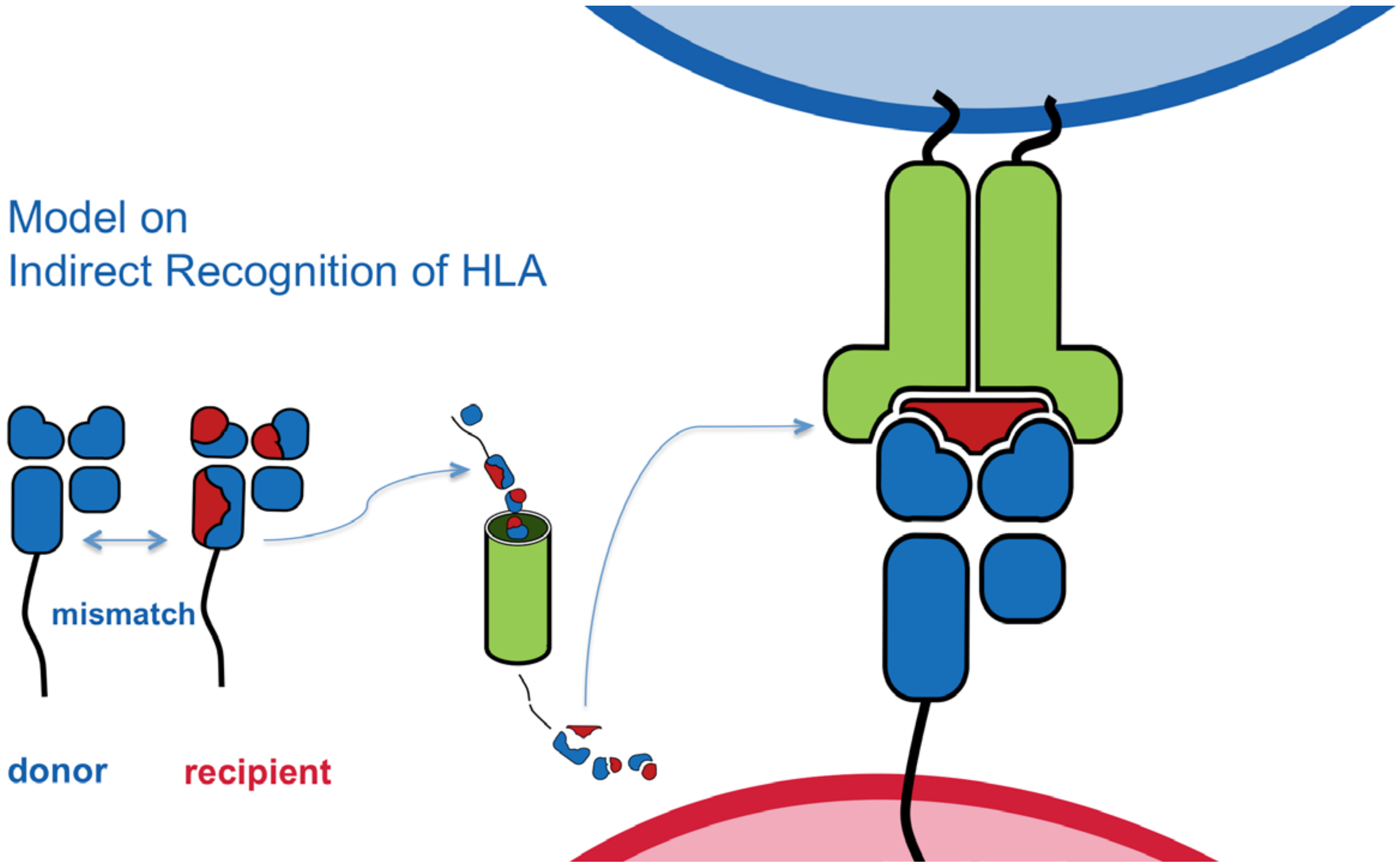
serologic match

PIRCHE

Eplets

- Essential components of HLA epitopes recognized by antibody
- Amino acid configurations within a 3 Angstrom radius of surface-exposed polymorphic residues
- Parts of “structural” HLA epitopes that contact the CDRs of antibody

Meccanismo indiretto di riconoscimento degli allo-antigeni da parte dei linfociti T



Il tessuto trapiantato introduce antigeni HLA non-self.

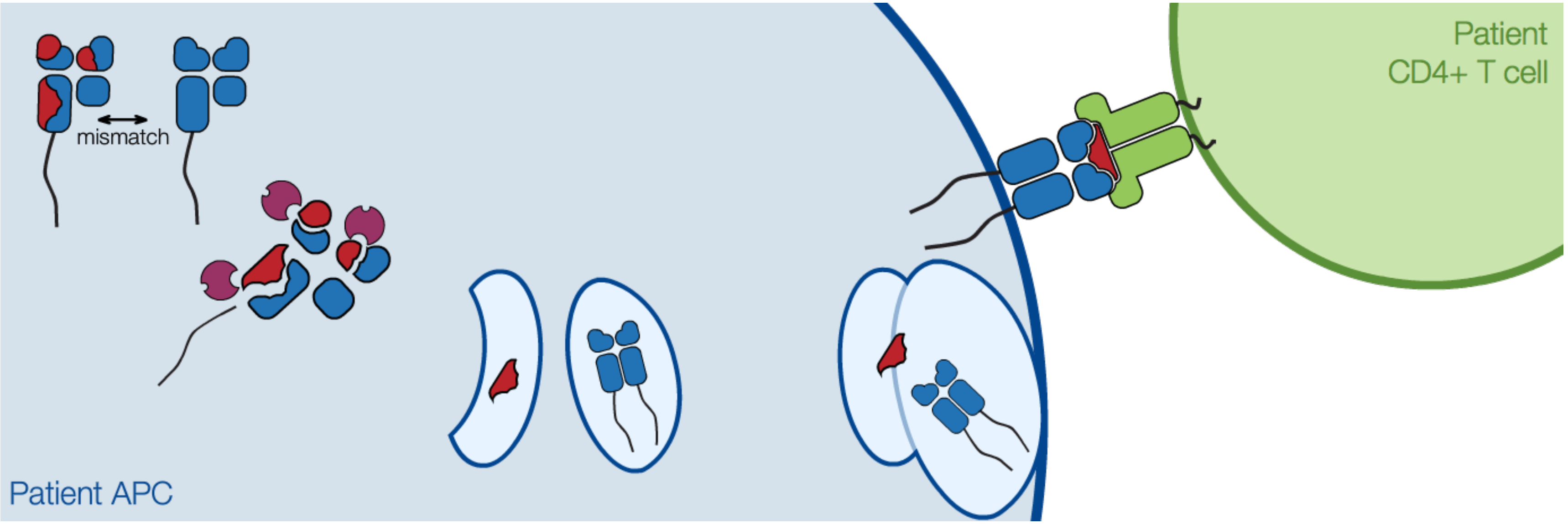
Nelle APC, queste proteine saranno processate nei lisosomi o altre strutture in peptidi più piccoli per poter essere presentati ai linfociti T dalle molecole HLA-self in forma immunologicamente utile.

La presenza di mismatch HLA tra ricevente e donatore, determina la attivazione dei linfociti T e la induzione della risposta immune

Potranno essere prodotti numerosi tipi di peptidi antigenici con differente affinità di legame e differente probabilità di essere presentati ai linfociti T e indurre la risposta immune

#PIRCHE = numero dei peptidi non-self

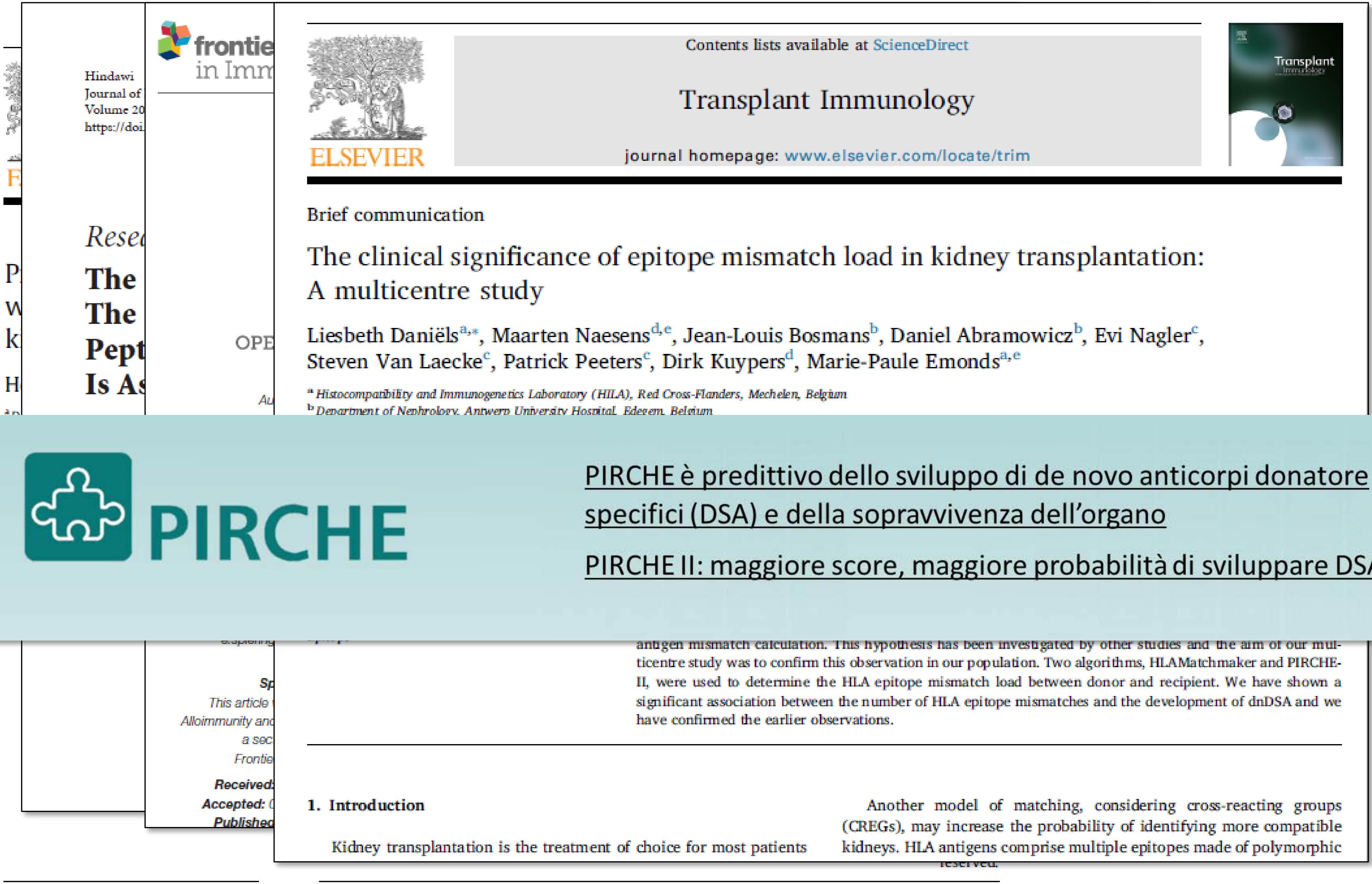
Trapianti di organi solidi (SOT): Kidney Transplantation



I linfociti T helper rispondono in modo specifico ai peptidi donor-mismatched presentati dalle molecole HLA di Classe II espresse sulle APC del ricevente, attivando una risposta immune.

I linfociti T attivati attraverso il rilascio di citochine, promuovono la proliferazione e la differenziazione delle cellule B a produrre anticorpi donatore specifici (DSA)

PIRCHE simula in modo efficace questo concetto e fornisce il numero di peptidi donor-mismatched, che possono essere rilevati dalle cellule T dei pazienti.



Contents lists available at ScienceDirect

Transplant Immunology

journal homepage: www.elsevier.com/locate/trim

Brief communication

The clinical significance of epitope mismatch load in kidney transplantation: A multicentre study

Liesbeth Daniëls[a,*], Maarten Naesens[d,e], Jean-Louis Bosmans[b], Daniel Abramowicz[b], Evi Nagler[c], Steven Van Laecke[c], Patrick Peeters[c], Dirk Kuypers[d], Marie-Paule Emonds[a,e]

[a] Histocompatibility and Immunogenetics Laboratory (HILA), Red Cross-Flanders, Mechelen, Belgium
[b] Department of Nephrology, Antwerp University Hospital, Edegem, Belgium

antigen mismatch calculation. This hypothesis has been investigated by other studies and the aim of our multicentre study was to confirm this observation in our population. Two algorithms, HLAMatchmaker and PIRCHE-II, were used to determine the HLA epitope mismatch load between donor and recipient. We have shown a significant association between the number of HLA epitope mismatches and the development of dnDSA and we have confirmed the earlier observations.

1. Introduction

Kidney transplantation is the treatment of choice for most patients

Another model of matching, considering cross-reacting groups (CREGs), may increase the probability of identifying more compatible kidneys. HLA antigens comprise multiple epitopes made of polymorphic

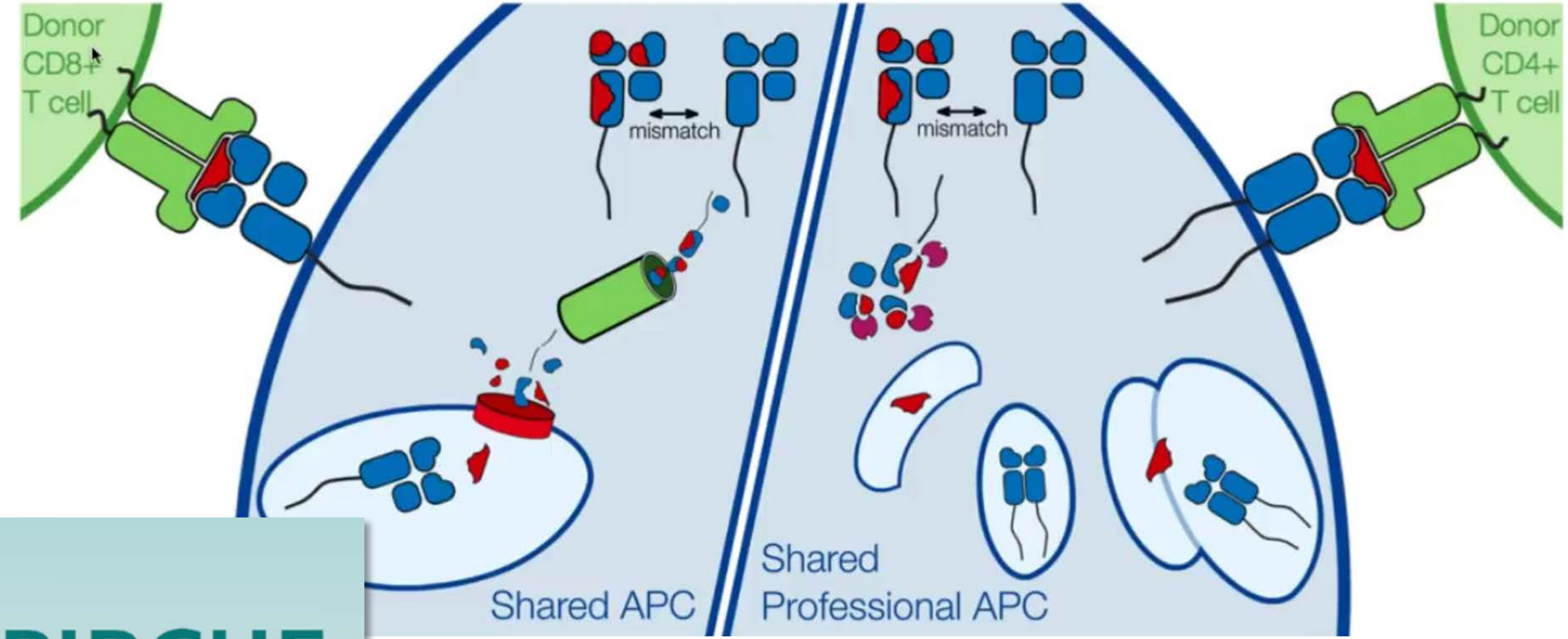
PIRCHE

PIRCHE è predittivo dello sviluppo di de novo anticorpi donatore specifici (DSA) e della sopravvivenza dell’organo

PIRCHE II: maggiore score, maggiore probabilità di sviluppare DSA

Trapianti di cellule staminali ematopoietiche (HSCT)

Cellule immunocompetenti in grado di riconoscere peptidi HLA non-self del paziente che possono indurre una risposta immunitaria mirata al paziente



PIRCHE

In SOT il PIRCHE predice il numero di peptidi donor-mismatch che possono essere rilevati dai linfociti T dei pazienti

In HSCT il PIRCHE predice il numero di peptidi mismatch dei pazienti che possono essere rilevati dai linfociti T del donatore.

Inserendo nel web le tipizzazioni dei pazienti e dei donatori, l'algoritmo PIRCHE® identifica i peptidi che possono essere riconosciuti come estranei dal sistema immunitario.

Più basso è il numero di tali peptidi (PIRCHEs), minore è l'incidenza della risposta immunitaria

PIRCHE I = numero dei PIRCHEs presentati da HLA I

PIRCHE II = numero dei PIRCHEs presentati da HLA II

PIRCHE

PIRCHE Web Service

https://www.pirche.org

L’applicazione PIRCHE web è disponibile a partire dal 24 luglio da qualsiasi computer con accesso a Internet.

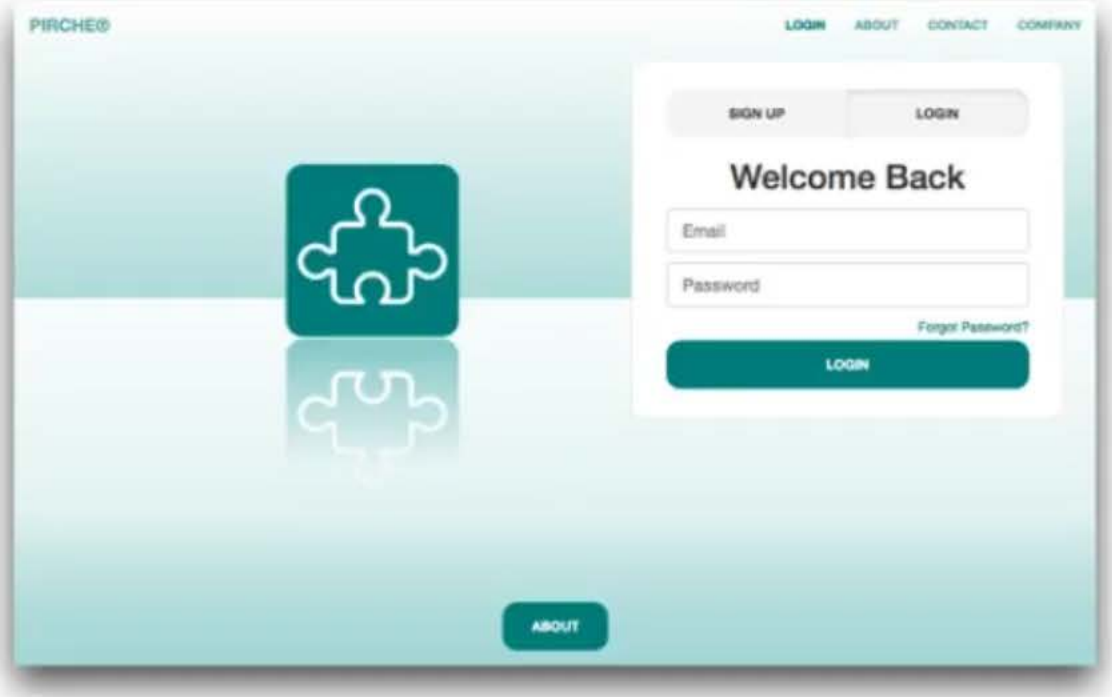
Non è necessario installare o gestire alcun software localmente

soddisfa tutti gli standard richiesti per la sicurezza dei dati.

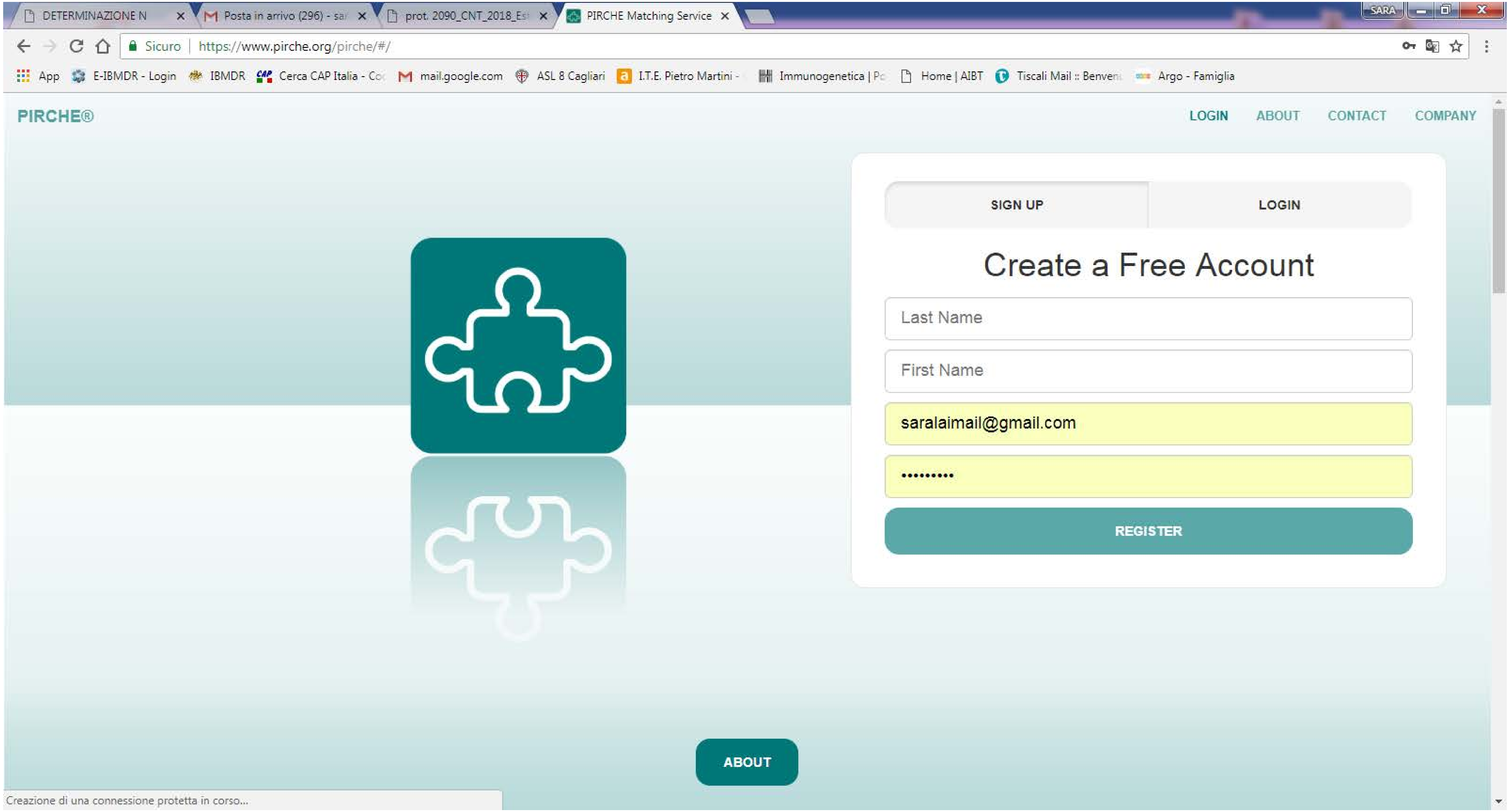
La tecnologia è stata convalidata da numerosi studi scientifici condotti su migliaia di pazienti e viene già utilizzata da numerose cliniche e laboratori leader nella pratica quotidiana.

La applicazione presente sul web è gratis: per i progetti di ricerca il matching service è libero.

La società concede la licenza della sua piattaforma a fornitori di prodotti e servizi nel campo del laboratorio clinico, ai registri dei donatori, alle organizzazioni di assegnazione degli organi e all'industria biofarmaceutica.



PIRCHE



https://www.pirche.org/pirche/#/

Create a Free Account

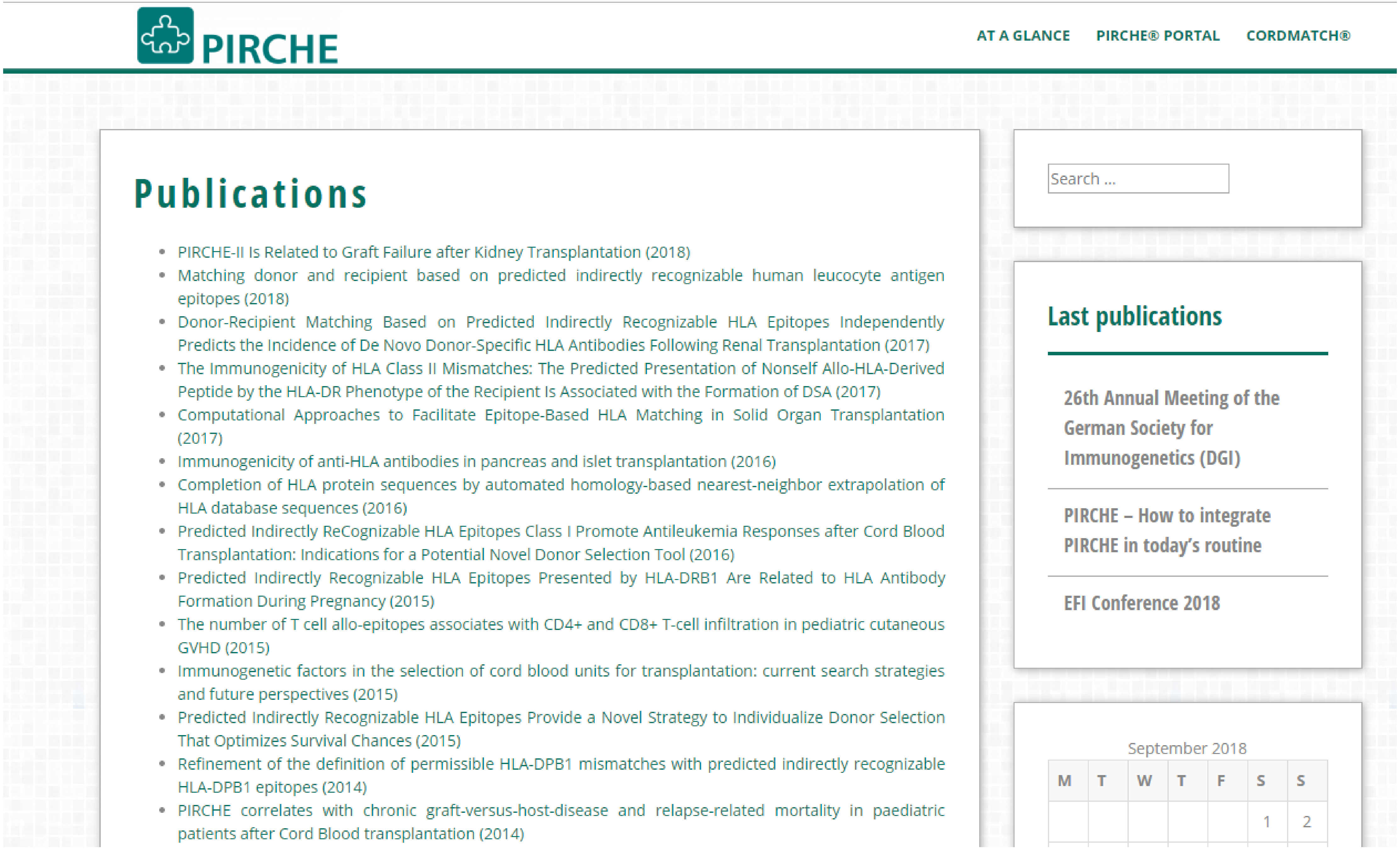
Last Name

First Name

saralaimail@gmail.com

•••••••••

Creazione di una connessione protetta in corso...



Publications

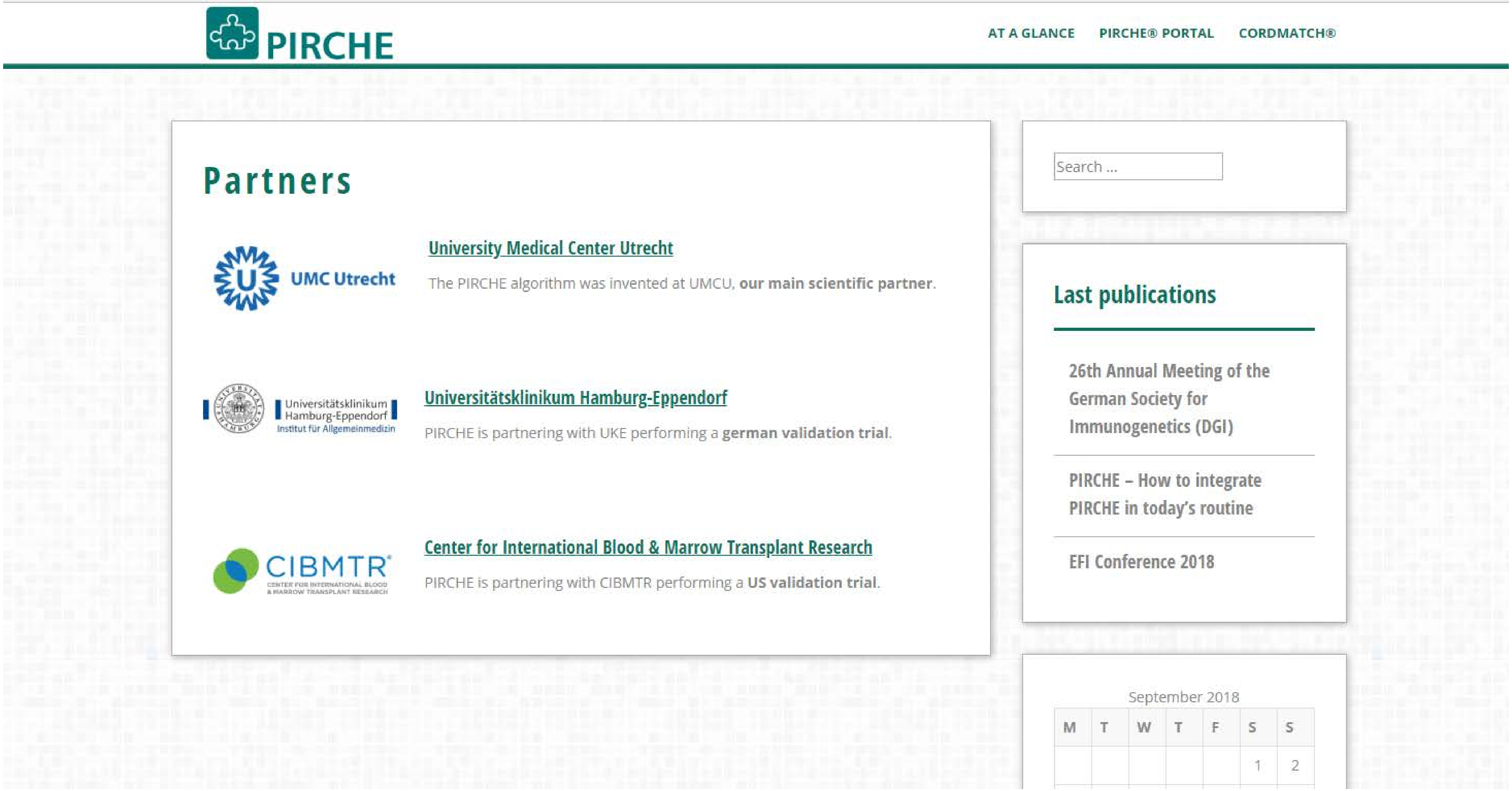
- PIRCHE-II Is Related to Graft Failure after Kidney Transplantation (2018)
- Matching donor and recipient based on predicted indirectly recognizable human leucocyte antigen epitopes (2018)
- Donor-Recipient Matching Based on Predicted Indirectly Recognizable HLA Epitopes Independently Predicts the Incidence of De Novo Donor-Specific HLA Antibodies Following Renal Transplantation (2017)
- The Immunogenicity of HLA Class II Mismatches: The Predicted Presentation of Nonself Allo-HLA-Derived Peptide by the HLA-DR Phenotype of the Recipient Is Associated with the Formation of DSA (2017)
- Computational Approaches to Facilitate Epitope-Based HLA Matching in Solid Organ Transplantation (2017)
- Immunogenicity of anti-HLA antibodies in pancreas and islet transplantation (2016)
- Completion of HLA protein sequences by automated homology-based nearest-neighbor extrapolation of HLA database sequences (2016)
- Predicted Indirectly ReCognizable HLA Epitopes Class I Promote Antileukemia Responses after Cord Blood Transplantation: Indications for a Potential Novel Donor Selection Tool (2016)
- Predicted Indirectly Recognizable HLA Epitopes Presented by HLA-DRB1 Are Related to HLA Antibody Formation During Pregnancy (2015)
- The number of T cell allo-epitopes associates with CD4+ and CD8+ T-cell infiltration in pediatric cutaneous GVHD (2015)
- Immunogenetic factors in the selection of cord blood units for transplantation: current search strategies and future perspectives (2015)
- Predicted Indirectly Recognizable HLA Epitopes Provide a Novel Strategy to Individualize Donor Selection That Optimizes Survival Chances (2015)
- Refinement of the definition of permissible HLA-DPB1 mismatches with predicted indirectly recognizable HLA-DPB1 epitopes (2014)
- PIRCHE correlates with chronic graft-versus-host-disease and relapse-related mortality in paediatric patients after Cord Blood transplantation (2014)

Last publications

- 26th Annual Meeting of the German Society for Immunogenetics (DGI)
- PIRCHE – How to integrate PIRCHE in today's routine
- EFI Conference 2018

September 2018

M	T	W	T	F	S	S
					1	2



Partners

University Medical Center Utrecht

The PIRCHE algorithm was invented at UMCU, **our main scientific partner**.

Universitätsklinikum Hamburg-Eppendorf

PIRCHE is partnering with UKE performing a **german validation trial**.

Center for International Blood & Marrow Transplant Research

PIRCHE is partnering with CIBMTR performing a **US validation trial**.

Last publications

- 26th Annual Meeting of the German Society for Immunogenetics (DGI)
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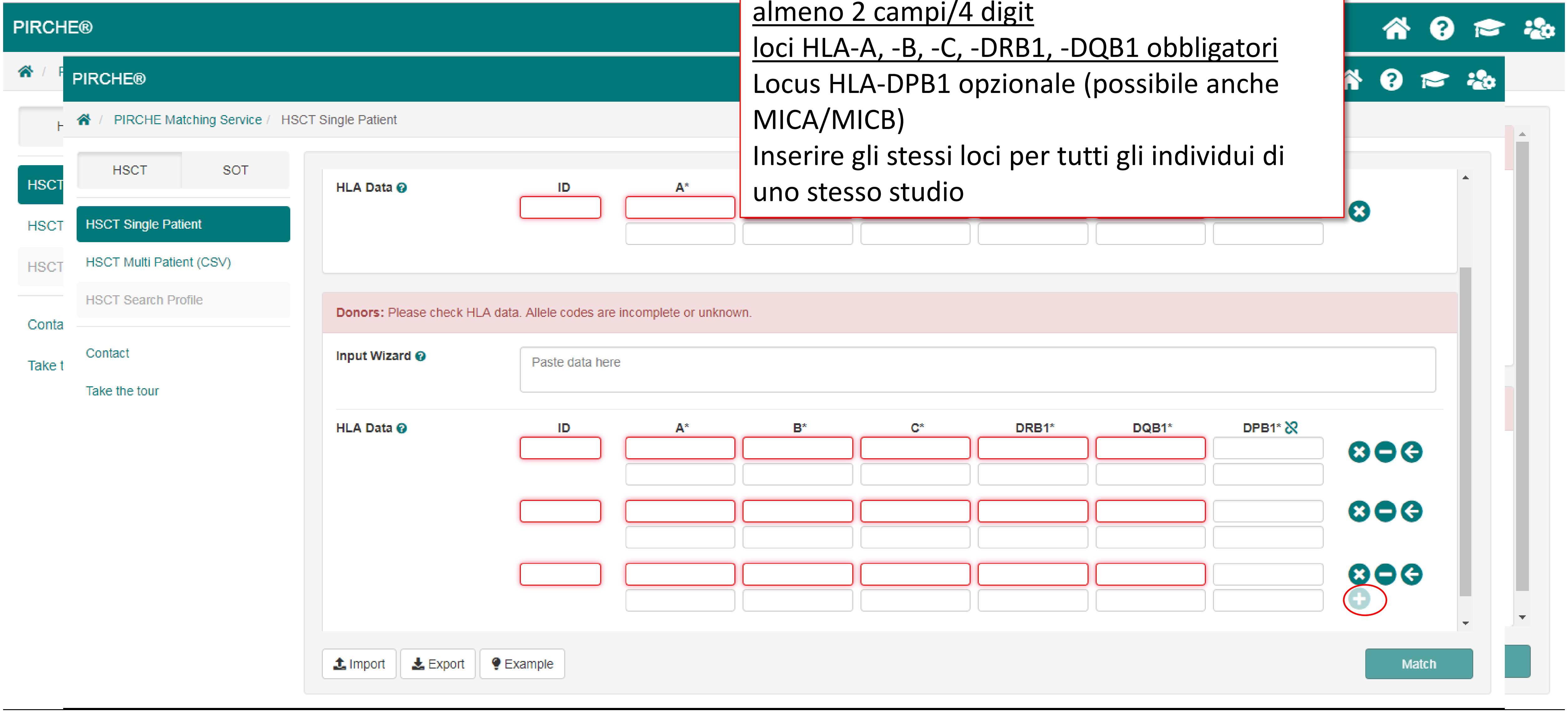
- EFI Conference 2018

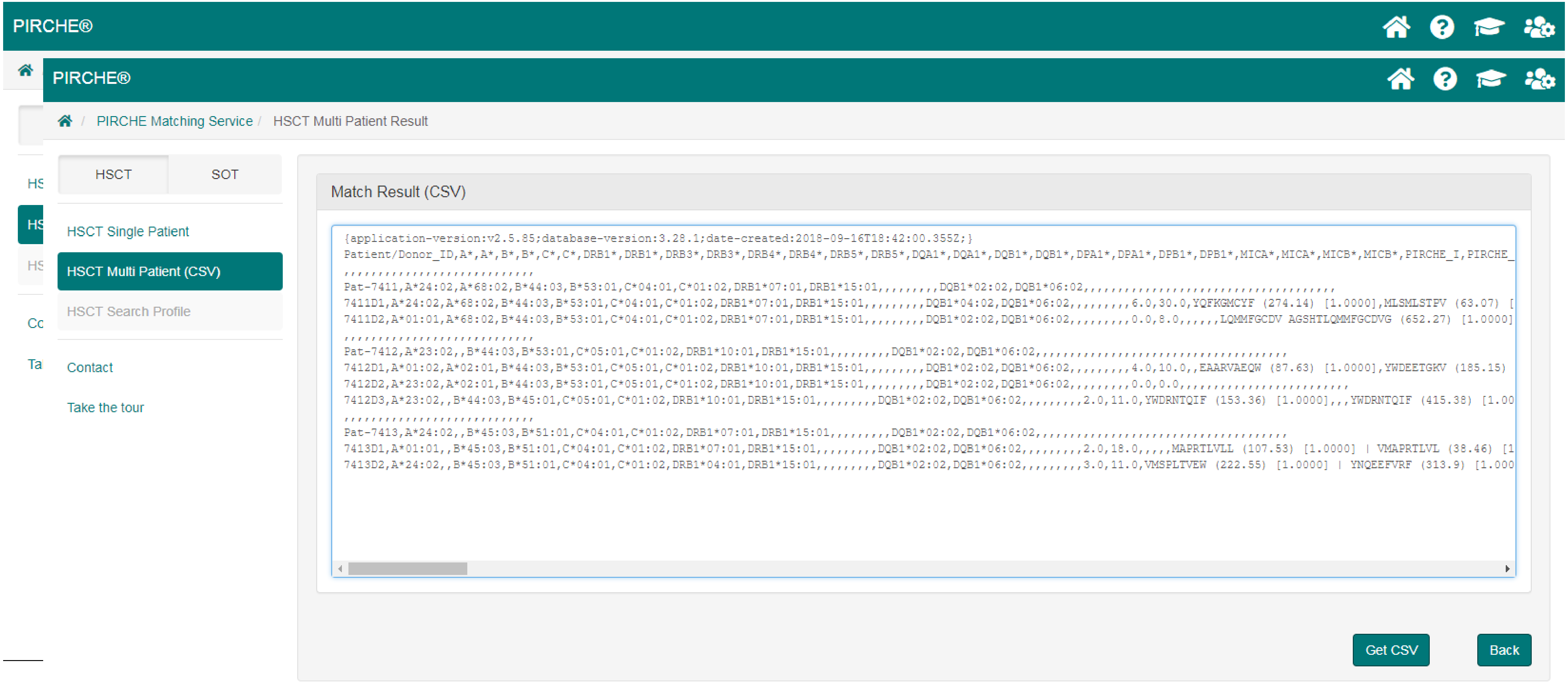
September 2018

M	T	W	T	F	S	S
					1	2

Tipizzazione molecolare in alta risoluzione:
almeno 2 campi/4 digit
loci HLA-A, -B, -C, -DRB1, -DQB1 obbligatori
Locus HLA-DPB1 opzionale (possibile anche MICA/MICB)
Inserire gli stessi loci per tutti gli individui di uno stesso studio



Donors: Please check HLA data. Allele codes are incomplete or unknown.



Match Result (CSV)

```
{application-version:v2.5.85;database-version:3.28.1;date-created:2018-09-16T18:42:00.355Z;}
Patient/Donor_ID,A*,A*,B*,B*,C*,C*,DRB1*,DRB1*,DRB3*,DRB3*,DRB4*,DRB4*,DRB5*,DRB5*,DQA1*,DQA1*,DQB1*,DQB1*,DPA1*,DPA1*,DPB1*,DPB1*,MICA*,MICA*,MICB*,MICB*,PIRCHE_I,PIRCHE_
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Pat-7411,A*24:02,A*68:02,B*44:03,B*53:01,C*04:01,C*01:02,DRB1*07:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
7411D1,A*24:02,A*68:02,B*44:03,B*53:01,C*04:01,C*01:02,DRB1*07:01,DRB1*15:01,,,,,,,,,DQB1*04:02,DQB1*06:02,,,,,,,,,6.0,30.0,YQFKGMCYF (274.14) [1.0000],MLSMLSTPV (63.07) [
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,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
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7412D1,A*01:02,A*02:01,B*44:03,B*53:01,C*05:01,C*01:02,DRB1*10:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,4.0,10.0,,EAARVAEQW (87.63) [1.0000],YWDEETGKV (185.15)
7412D2,A*23:02,A*02:01,B*44:03,B*53:01,C*05:01,C*01:02,DRB1*10:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,0.0,0.0,,,,,,,,,,,,,,,,,,,,,,,,,
7412D3,A*23:02,,B*44:03,B*45:01,C*05:01,C*01:02,DRB1*10:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,2.0,11.0,YWDRNTQIF (153.36) [1.0000],,,YWDRNTQIF (415.38) [1.00
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Pat-7413,A*24:02,,B*45:03,B*51:01,C*04:01,C*01:02,DRB1*07:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
7413D1,A*01:01,,B*45:03,B*51:01,C*04:01,C*01:02,DRB1*07:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,2.0,18.0,,,,MAPRTLVLL (107.53) [1.0000] | VMAPRTLVL (38.46) [1
7413D2,A*24:02,,B*45:03,B*51:01,C*04:01,C*01:02,DRB1*04:01,DRB1*15:01,,,,,,,,,DQB1*02:02,DQB1*06:02,,,,,,,,,3.0,11.0,VMSPLTVEW (222.55) [1.0000] | YNQEEFVRF (313.9) [1.000
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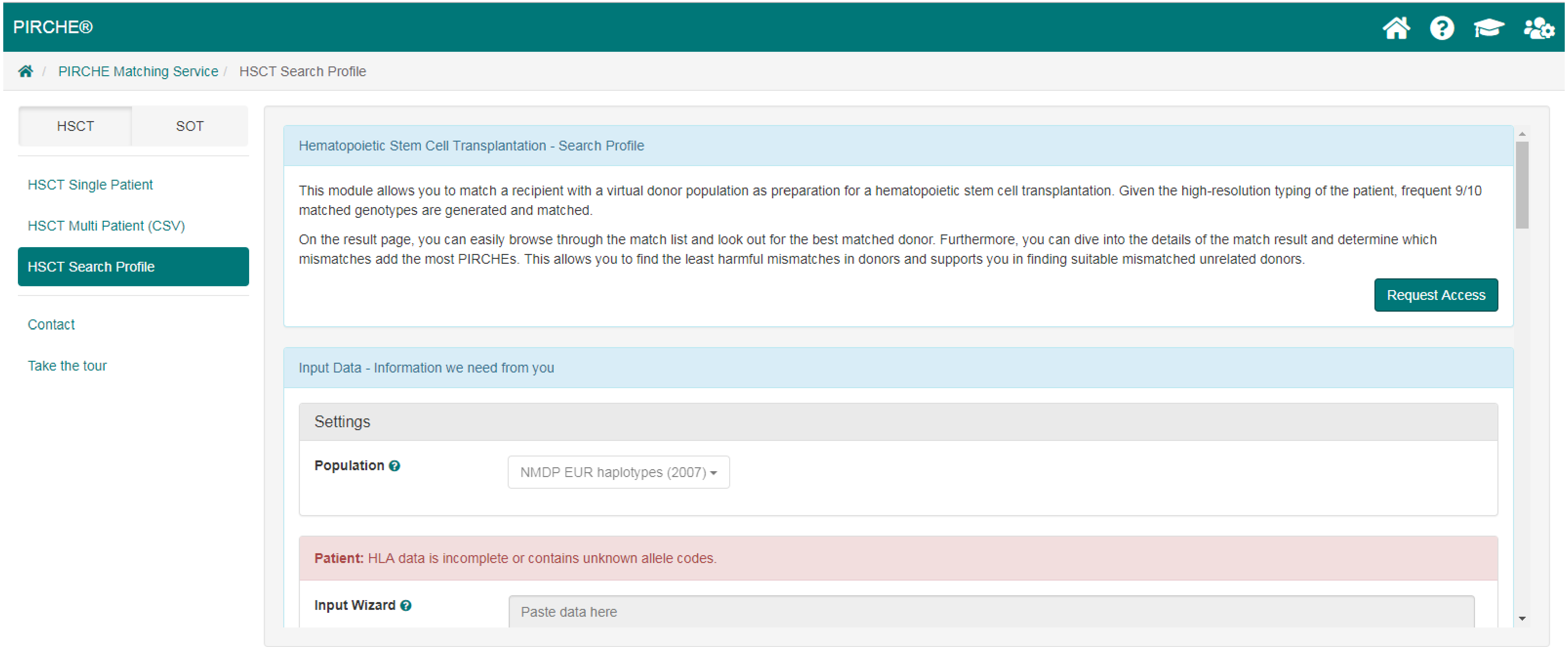


Hematopoietic Stem Cell Transplantation - Search Profile

This module allows you to match a recipient with a virtual donor population as preparation for a hematopoietic stem cell transplantation. Given the high-resolution typing of the patient, frequent 9/10 matched genotypes are generated and matched.

On the result page, you can easily browse through the match list and look out for the best matched donor. Furthermore, you can dive into the details of the match result and determine which mismatches add the most PIRCHEs. This allows you to find the least harmful mismatches in donors and supports you in finding suitable mismatched unrelated donors.

Input Data - Information we need from you

Settings

Population NMDP EUR haplotypes (2007)

Patient: HLA data is incomplete or contains unknown allele codes.

Input Wizard Paste data here

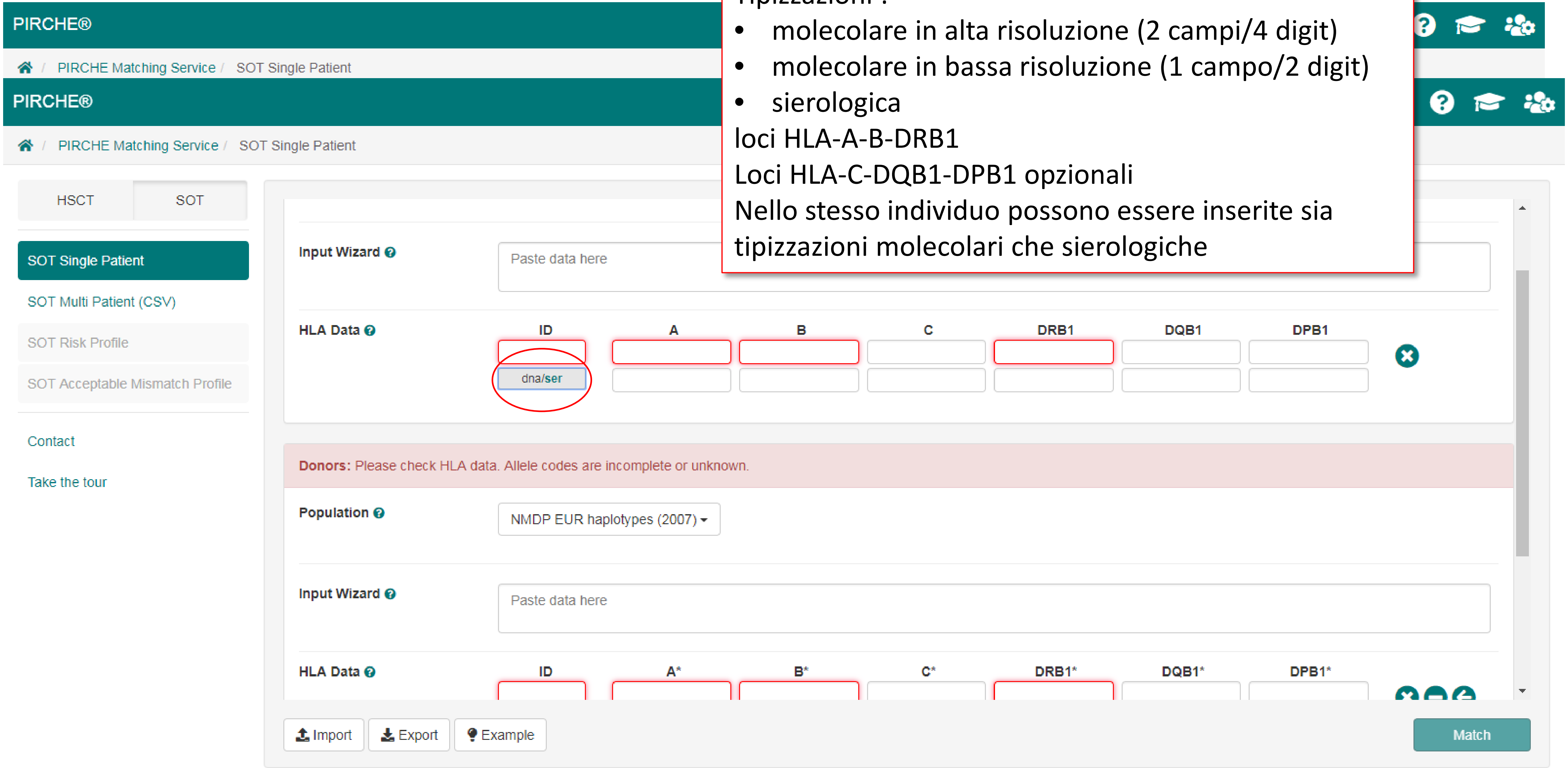
Tipizzazioni :

- molecolare in alta risoluzione (2 campi/4 digit)
- molecolare in bassa risoluzione (1 campo/2 digit)
- sierologica

loci HLA-A-B-DRB1

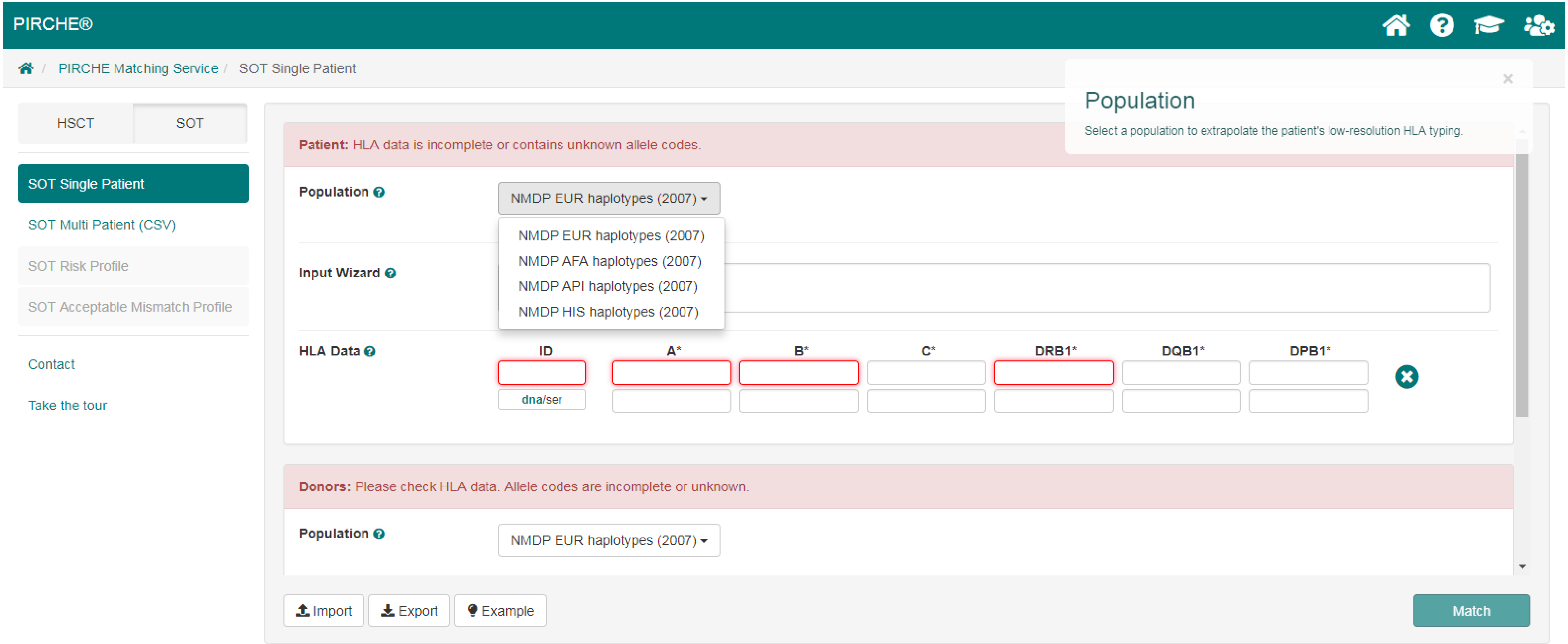
Loci HLA-C-DQB1-DPB1 opzionali

Nello stesso individuo possono essere inserite sia tipizzazioni molecolari che sierologiche



Donors: Please check HLA data. Allele codes are incomplete or unknown.

Population: NMDP EUR haplotypes (2007)



Population

Select a population to extrapolate the patient's low-resolution HLA typing.

Patient: HLA data is incomplete or contains unknown allele codes.

Population NMDP EUR haplotypes (2007)

- NMDP EUR haplotypes (2007)
- NMDP AFA haplotypes (2007)
- NMDP API haplotypes (2007)
- NMDP HIS haplotypes (2007)

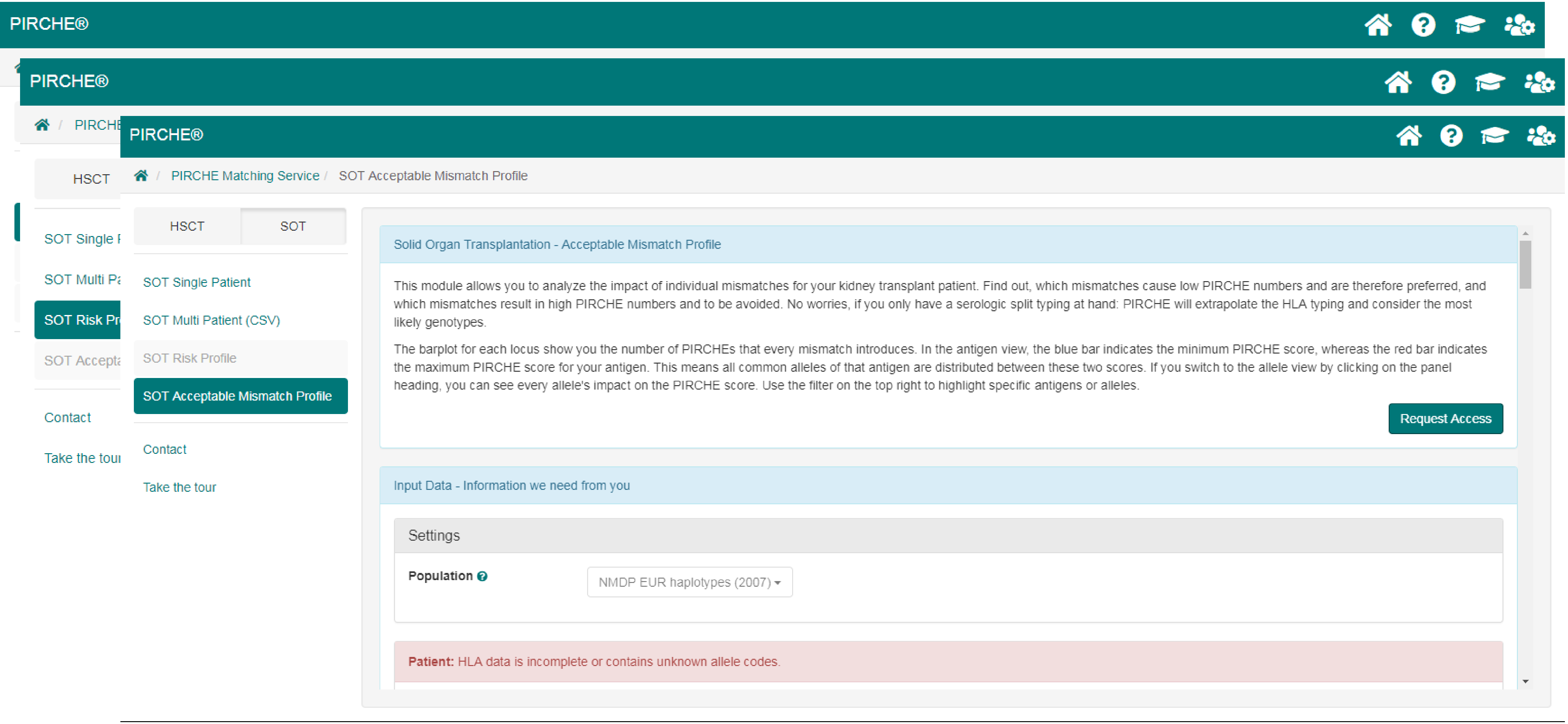
Input Wizard

HLA Data

ID	A*	B*	C*	DRB1*	DQB1*	DPB1*
dna/ser						

Donors: Please check HLA data. Allele codes are incomplete or unknown.

Population NMDP EUR haplotypes (2007)



PIRCHE Matching Service / SOT Acceptable Mismatch Profile

Solid Organ Transplantation - Acceptable Mismatch Profile

This module allows you to analyze the impact of individual mismatches for your kidney transplant patient. Find out, which mismatches cause low PIRCHE numbers and are therefore preferred, and which mismatches result in high PIRCHE numbers and to be avoided. No worries, if you only have a serologic split typing at hand: PIRCHE will extrapolate the HLA typing and consider the most likely genotypes.

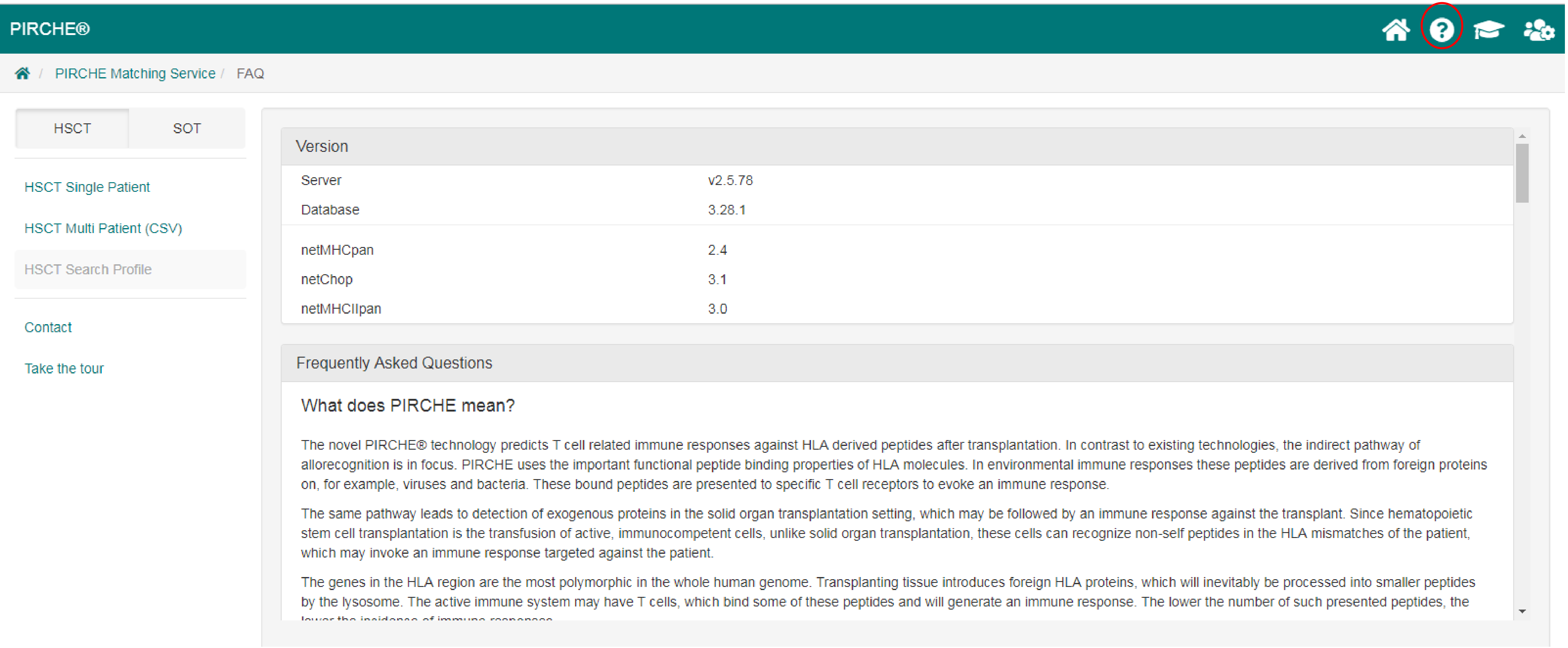
The barplot for each locus show you the number of PIRCHEs that every mismatch introduces. In the antigen view, the blue bar indicates the minimum PIRCHE score, whereas the red bar indicates the maximum PIRCHE score for your antigen. This means all common alleles of that antigen are distributed between these two scores. If you switch to the allele view by clicking on the panel heading, you can see every allele's impact on the PIRCHE score. Use the filter on the top right to highlight specific antigens or alleles.

Input Data - Information we need from you

Settings

Population NMDP EUR haplotypes (2007)

Patient: HLA data is incomplete or contains unknown allele codes.



Version

Server	v2.5.78
Database	3.28.1
netMHCpan	2.4
netChop	3.1
netMHCIIpan	3.0

Frequently Asked Questions

What does PIRCHE mean?

The novel PIRCHE® technology predicts T cell related immune responses against HLA derived peptides after transplantation. In contrast to existing technologies, the indirect pathway of allorecognition is in focus. PIRCHE uses the important functional peptide binding properties of HLA molecules. In environmental immune responses these peptides are derived from foreign proteins on, for example, viruses and bacteria. These bound peptides are presented to specific T cell receptors to evoke an immune response.

The same pathway leads to detection of exogenous proteins in the solid organ transplantation setting, which may be followed by an immune response against the transplant. Since hematopoietic stem cell transplantation is the transfusion of active, immunocompetent cells, unlike solid organ transplantation, these cells can recognize non-self peptides in the HLA mismatches of the patient, which may invoke an immune response targeted against the patient.

The genes in the HLA region are the most polymorphic in the whole human genome. Transplanting tissue introduces foreign HLA proteins, which will inevitably be processed into smaller peptides by the lysosome. The active immune system may have T cells, which bind some of these peptides and will generate an immune response. The lower the number of such presented peptides, the

What does PIRCHE mean?

What does HSCT and SOT mean?

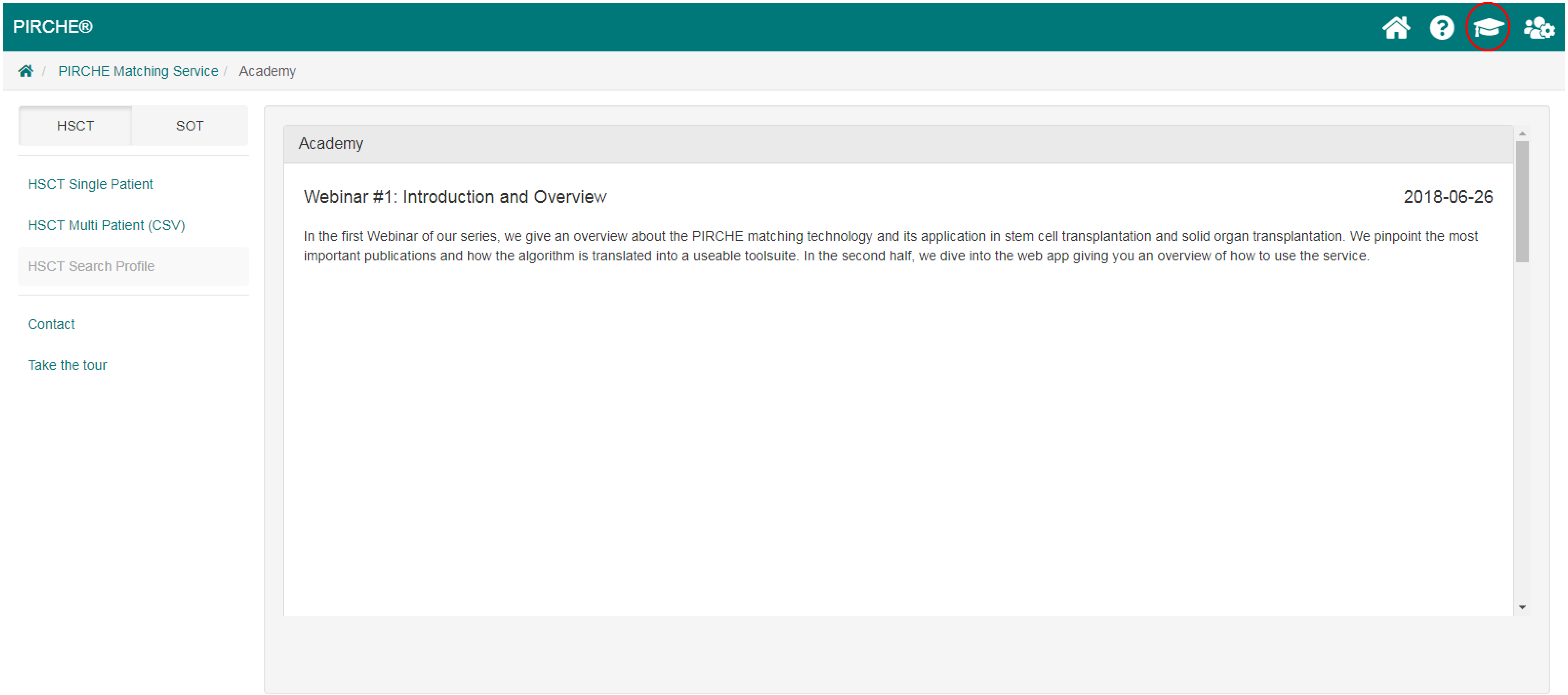
What does “Single Patient” vs. “Multi Patient (CSV)” mean?

What HLA typing resolution is required for PIRCHE analysis?

What formats are supported by the input wizard?

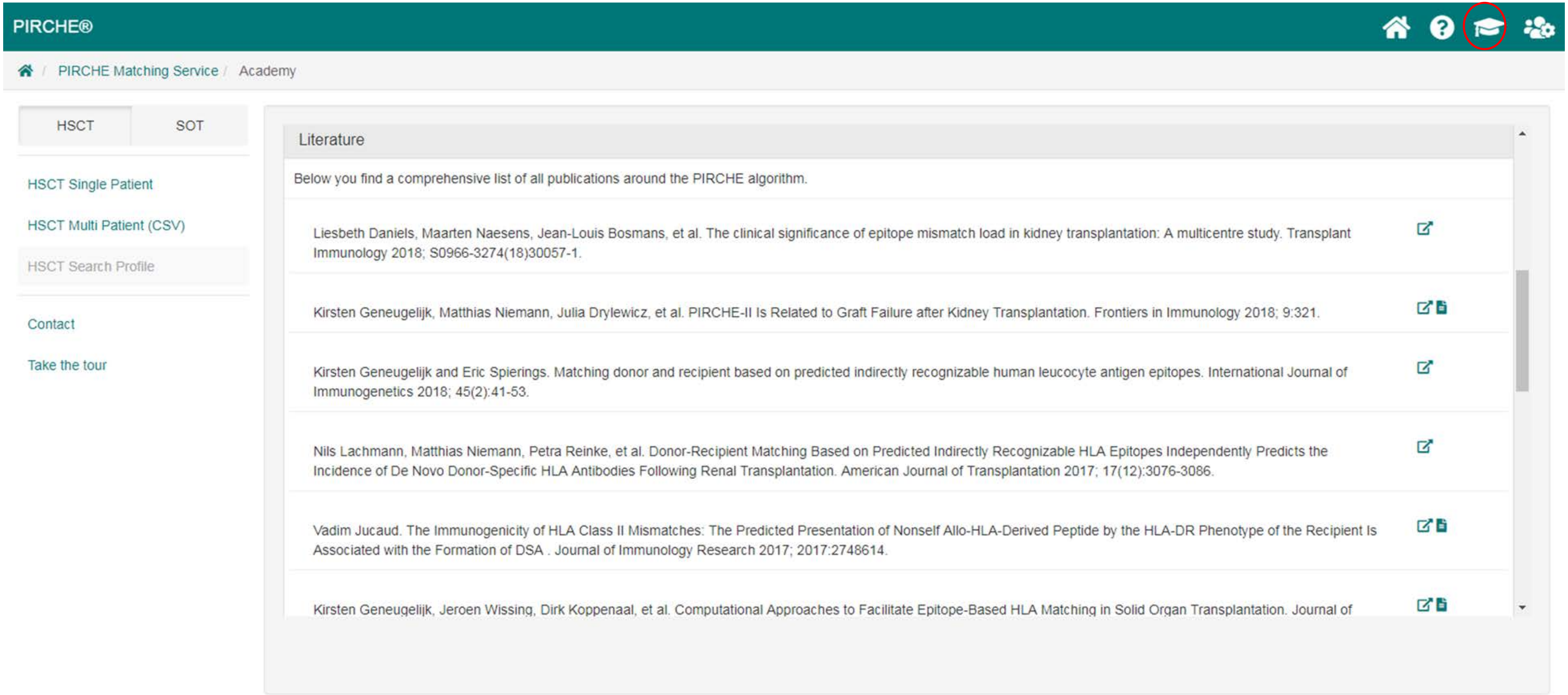
How to enter patient and donor data in "Multi Patient (CSV)" mode?

Can I see details of the PIRCHE analysis?



Webinar #1: Introduction and Overview 2018-06-26

In the first Webinar of our series, we give an overview about the PIRCHE matching technology and its application in stem cell transplantation and solid organ transplantation. We pinpoint the most important publications and how the algorithm is translated into a useable toolsuite. In the second half, we dive into the web app giving you an overview of how to use the service.



Literature

Below you find a comprehensive list of all publications around the PIRCHE algorithm.

Liesbeth Daniels, Maarten Naesens, Jean-Louis Bosmans, et al. The clinical significance of epitope mismatch load in kidney transplantation: A multicentre study. Transplant Immunology 2018; S0966-3274(18)30057-1.

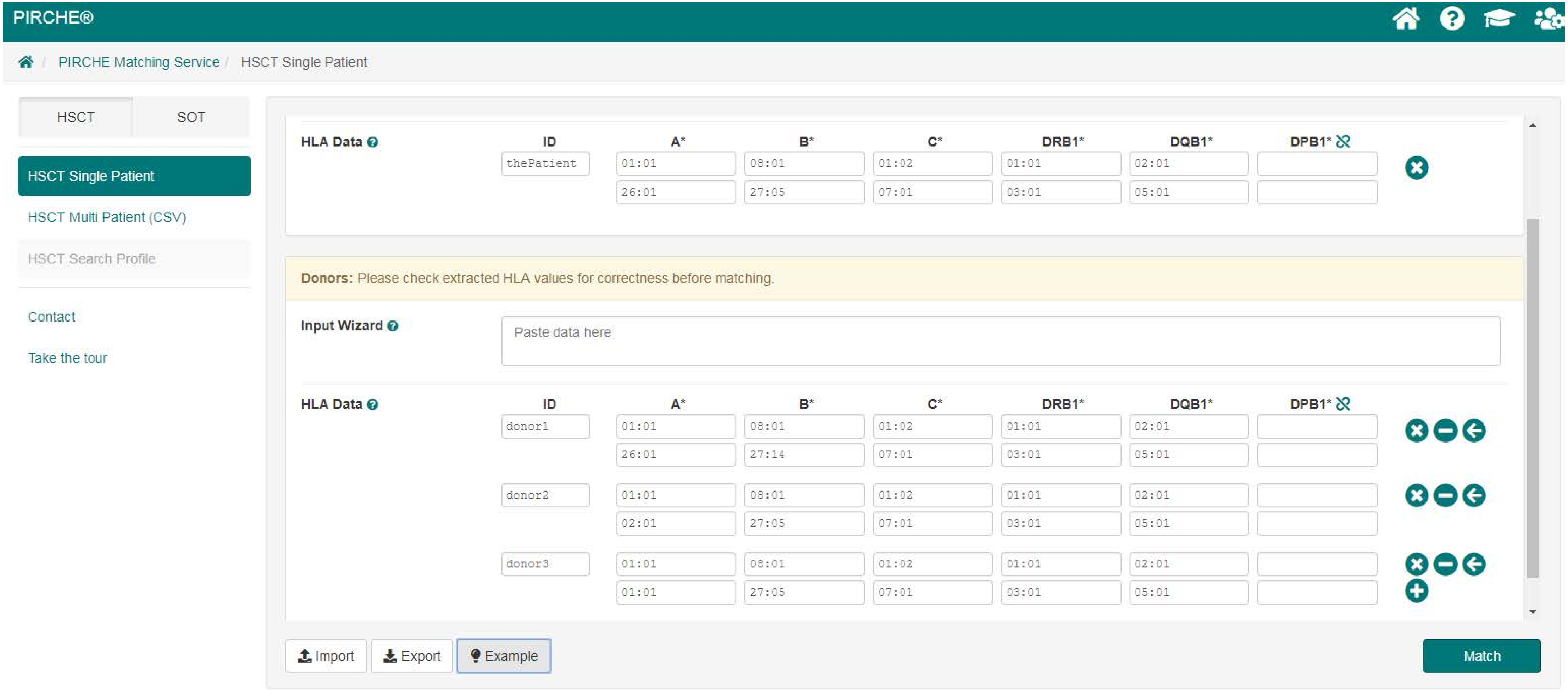
Kirsten Geneugelijk, Matthias Niemann, Julia Drylewicz, et al. PIRCHE-II Is Related to Graft Failure after Kidney Transplantation. Frontiers in Immunology 2018; 9:321.

Kirsten Geneugelijk and Eric Spierings. Matching donor and recipient based on predicted indirectly recognizable human leucocyte antigen epitopes. International Journal of Immunogenetics 2018; 45(2):41-53.

Nils Lachmann, Matthias Niemann, Petra Reinke, et al. Donor-Recipient Matching Based on Predicted Indirectly Recognizable HLA Epitopes Independently Predicts the Incidence of De Novo Donor-Specific HLA Antibodies Following Renal Transplantation. American Journal of Transplantation 2017; 17(12):3076-3086.

Vadim Jucaud. The Immunogenicity of HLA Class II Mismatches: The Predicted Presentation of Nonself Allo-HLA-Derived Peptide by the HLA-DR Phenotype of the Recipient Is Associated with the Formation of DSA . Journal of Immunology Research 2017; 2017:2748614.

Kirsten Geneugelijk, Jeroen Wissing, Dirk Koppenaal, et al. Computational Approaches to Facilitate Epitope-Based HLA Matching in Solid Organ Transplantation. Journal of



HLA Data

ID	A*	B*	C*	DRB1*	DQB1*	DPB1*
thePatient	01:01	08:01	01:02	01:01	02:01	
	26:01	27:05	07:01	03:01	05:01	

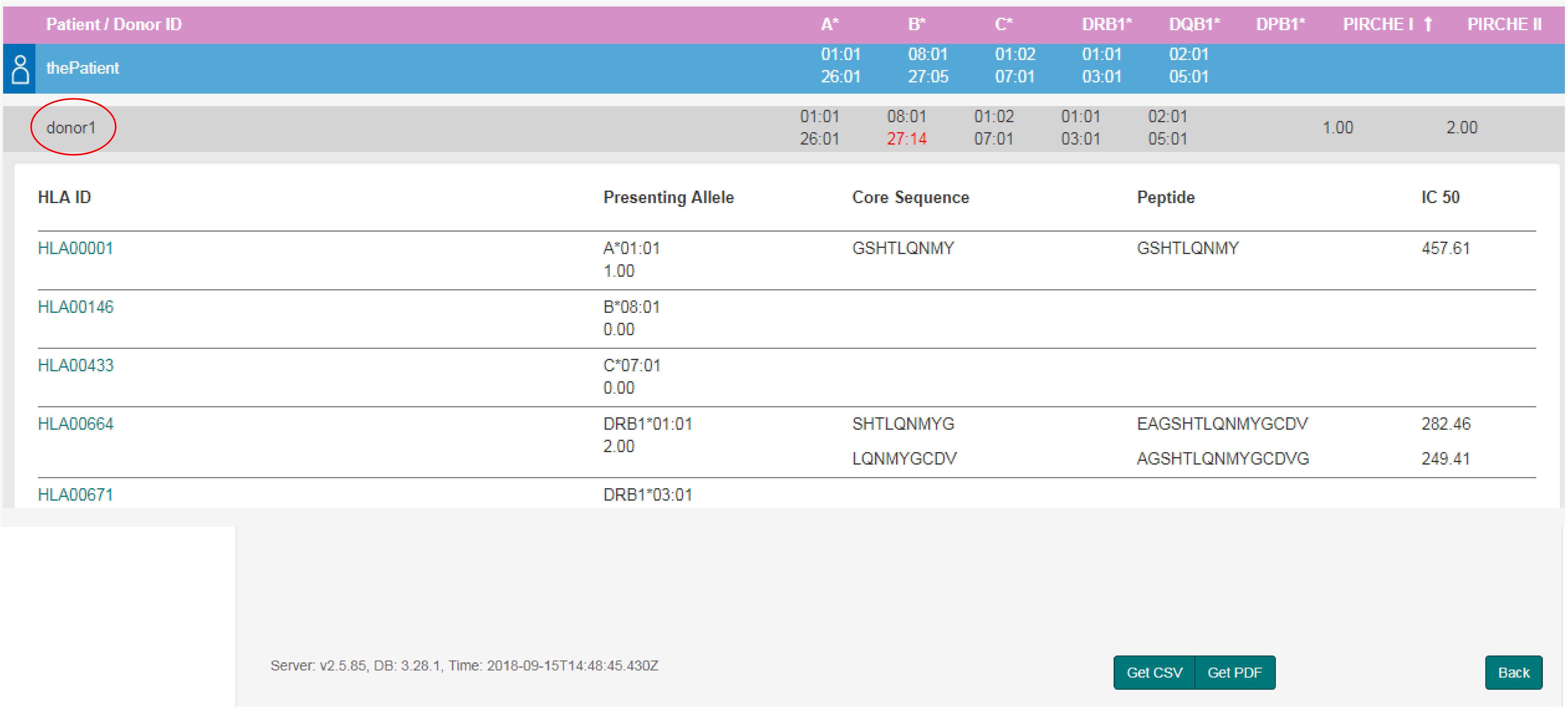
Donors: Please check extracted HLA values for correctness before matching.

Input Wizard

Paste data here

HLA Data

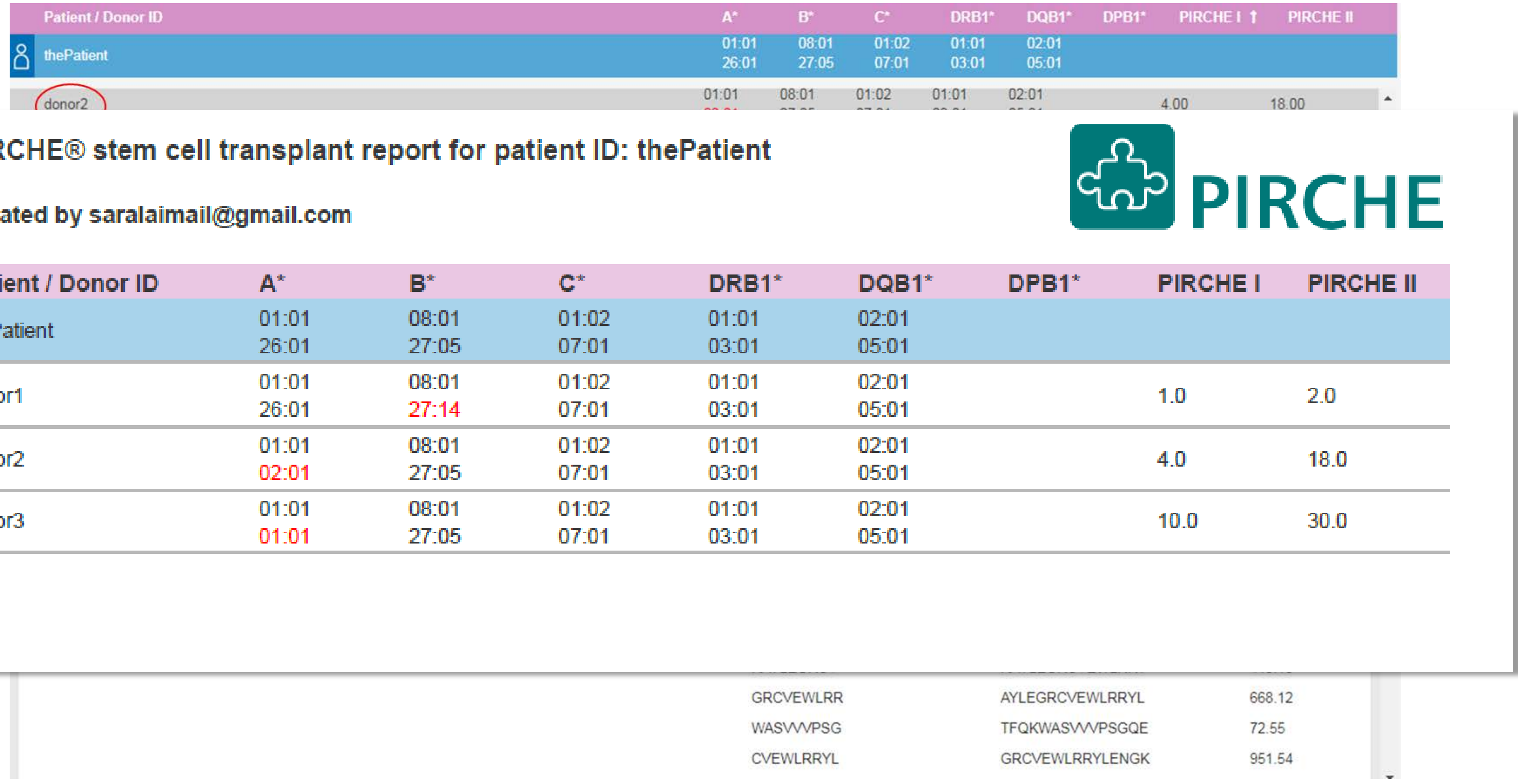
ID	A*	B*	C*	DRB1*	DQB1*	DPB1*
donor1	01:01	08:01	01:02	01:01	02:01	
	26:01	27:14	07:01	03:01	05:01	
donor2	01:01	08:01	01:02	01:01	02:01	
	02:01	27:05	07:01	03:01	05:01	
donor3	01:01	08:01	01:02	01:01	02:01	
	01:01	27:05	07:01	03:01	05:01	



Patient / Donor ID	A*	B*	C*	DRB1*	DQB1*	DPB1*	PIRCHE I ↑	PIRCHE II
thePatient	01:01 26:01	08:01 27:05	01:02 07:01	01:01 03:01	02:01 05:01			
donor1	01:01 26:01	08:01 27:14	01:02 07:01	01:01 03:01	02:01 05:01		1.00	2.00

HLA ID	Presenting Allele	Core Sequence	Peptide	IC 50
HLA00001	A*01:01 1.00	GSHTLQNMY	GSHTLQNMY	457.61
HLA00146	B*08:01 0.00			
HLA00433	C*07:01 0.00			
HLA00664	DRB1*01:01 2.00	SHTLQNMYG LQNMYGCDV	EAGSHTLQNMYGCDV AGSHTLQNMYGCDVG	282.46 249.41
HLA00671	DRB1*03:01			

Server: v2.5.85, DB: 3.28.1, Time: 2018-09-15T14:48:45.430Z



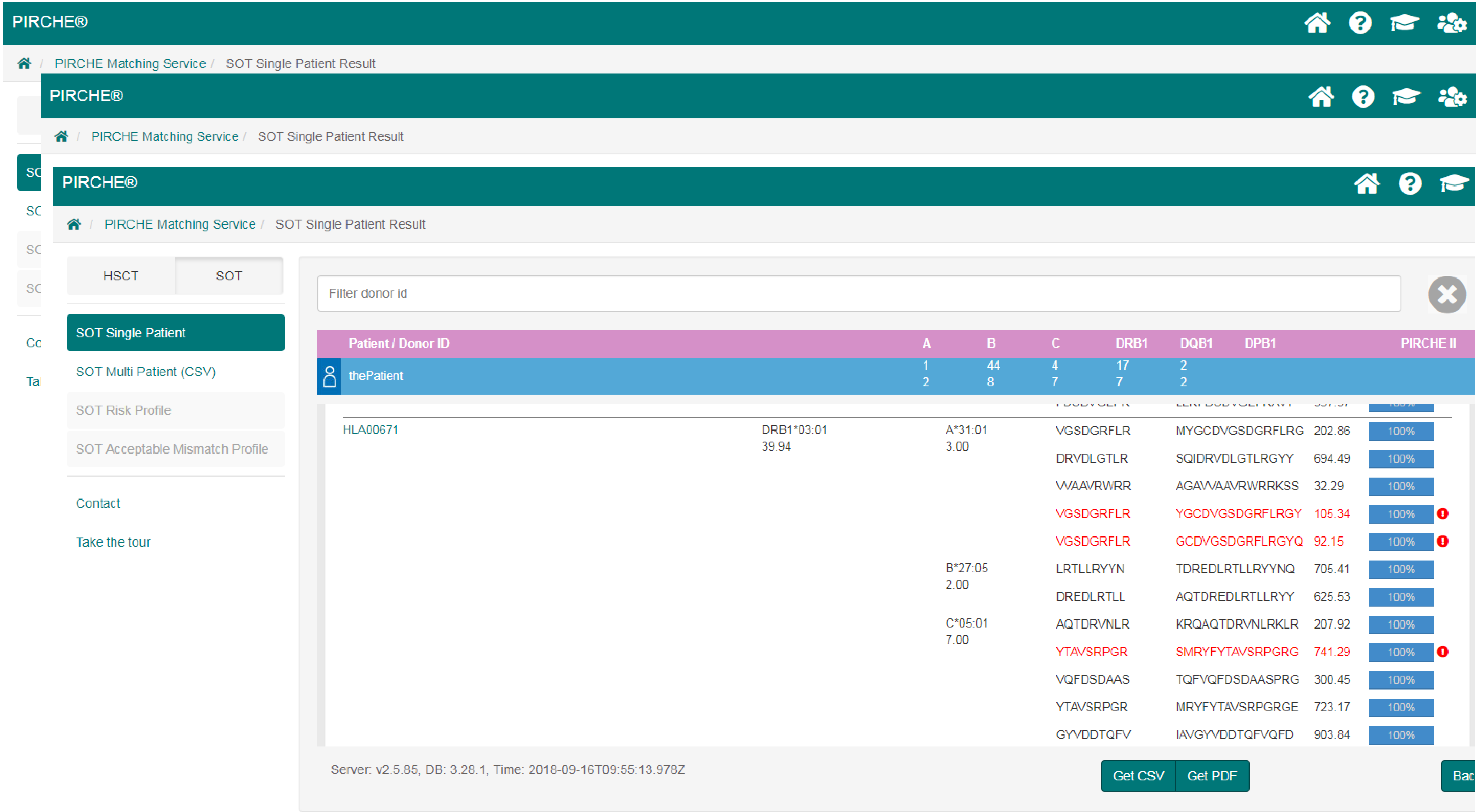
Patient / Donor ID	A*	B*	C*	DRB1*	DQB1*	DPB1*	PIRCHE I ↑	PIRCHE II
thePatient	01:01 26:01	08:01 27:05	01:02 07:01	01:01 03:01	02:01 05:01			
donor2	01:01	08:01	01:02	01:01	02:01		4.00	18.00

PIRCHE® stem cell transplant report for patient ID: thePatient

Created by saralaimail@gmail.com

Patient / Donor ID	A*	B*	C*	DRB1*	DQB1*	DPB1*	PIRCHE I	PIRCHE II
thePatient	01:01 26:01	08:01 27:05	01:02 07:01	01:01 03:01	02:01 05:01			
donor1	01:01 26:01	08:01 27:14	01:02 07:01	01:01 03:01	02:01 05:01		1.0	2.0
donor2	01:01 02:01	08:01 27:05	01:02 07:01	01:01 03:01	02:01 05:01		4.0	18.0
donor3	01:01 01:01	08:01 27:05	01:02 07:01	01:01 03:01	02:01 05:01		10.0	30.0

GRCVEWLRR	AYLEGRCVEWLRRYL	668.12
WASVVVPSG	TFQKWASVVVPSGQE	72.55
CVEWLRRYL	GRCVEWLRRYLENGK	951.54



Patient / Donor ID	A	B	C	DRB1	DQB1	DPB1	PIRCHE II
thePatient	1 2	44 8	4 7	17 7	2 2		

HLA00671	DRB1*03:01 39.94	A*31:01 3.00	VGSDGRFLR	MYGCDVGSDGRFLRG	202.86	100%	
			DRVDLGTLR	SQIDRVDLGTLRGYY	694.49	100%	
			VVAAVRWRR	AGAVVAAVRWRRKSS	32.29	100%	
			VGSDGRFLR	YGCDVGSDGRFLRGY	105.34	100%	❗
			VGSDGRFLR	GCDVGSDGRFLRGYQ	92.15	100%	❗
		B*27:05 2.00	LRTLLRYYN	TDREDLRTLLRYYNQ	705.41	100%	
			DREDLRTLL	AQTDREDLRTLLRYY	625.53	100%	
		C*05:01 7.00	AQTDRVNLR	KRQAQTDRVNLRKLR	207.92	100%	
			YTAVSRPGR	SMRYFYTAVSRPGRG	741.29	100%	❗
			VQFDSDAAS	TQFVQFDSDAASPRG	300.45	100%	
			YTAVSRPGR	MRYFYTAVSRPGRGE	723.17	100%	
			GYVDDTQFV	IAVGYVDDTQFVQFD	903.84	100%	

Server: v2.5.85, DB: 3.28.1, Time: 2018-09-16T09:55:13.978Z

PIRCHE Modules

- Predittivo del rischio di sviluppo di GVHD
- Consente di selezionare il donatore con il mismatch più permissivo

- Predittivo dello sviluppo di de novo anticorpi donatore specifici (DSA)
- Consente di identificare i trapianti ad alto rischio

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