A pilot study for the integration of cytometry reports in digital cytology telemedicine applications

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Summary. Up to date, tele-pathology in the three different forms of application, "dynamic", "static" and "virtual microscopy" has been mainly based on tele-hystology remote consulting. Today the diffusion of specialized WAN connections is guiding the research of new applications of tele-pathology. A specific analysis has been conducted, focused on digital cytology, in the biomedical laboratory of Sant'Andrea Hospital to investigate the technologies potentially useful to integrate in the LAN/WAN for telemedicine applications. Among the possible tools useful to be integrated in the LAN/WAN for telemedicine applications, the cytometry equipment available in the technical unity of cytometry has been considered important. The study finally provides a proposal for a tele-consulting architecture for the integration of cytometry reports both in the hospital LAN and the WAN for possible cooperative diagnosis and second opinion support.

Key words: telemedicine, digital cytology, flow citometry.

Riassunto (*Uno studio pilota per l'integrazione dei report citometrici nelle applicazioni di telemedicina in citologia digitale*). Fino ad oggi la tele-patologia nelle tre forme differenti "dinamica" "statica" e "di microscopia virtuale" si è principalmente basata sulla tele-istologia e sul teleconsulto a distanza. Oggi la diffusione di collegamenti dedicati WAN sta rendendo ipotizzabile l'uso di nuove applicazioni della tele-patologia. Un'analisi specifica è stata condotta, nell'ambito della citologia digitale, nel laboratorio biomedico dell'ospedale Sant'Andrea di Roma per studiare le tecnologie potenzialmente utili per integrare nella LAN/WAN alcuni sistemi biomedici in applicazioni di telemedicina. Tra i sistemi utili ad essere integrati nella WAN e LAN per le applicazioni di telemedicina è stato considerato il citometro a flusso, disponibile nell'unità tecnica di citometria. Lo studio infine fornisce una proposta per un'architettura di tele-consulto per l'integrazione dei report di citometria a flusso sia nella LAN dell'ospedale che nella WAN per la diagnosi cooperativa e/o il supporto di una second-opinion.

Parole chiave: telemedicina, citologia digitale, citometria a flusso.

INTRODUCTION

Up to date, tele-pathology in the three different forms of application, "dynamic", "static" and "virtual microscopy"[1-3] has been mainly based on tele-hystology remote consulting. The diffusion of specialized WAN connections (such as the Alleanza Ospedali Italiani nel Mondo, AOINM, which provides a service for remote consulting and e-learning for a net of Italian hospitals in the world. See http://www.ipocm.ministerosalute.it/) is guiding the research of new applications of the tele-pathology which are discussed in the monographic section of this issue of *Annali* dedicated to digital cytology [4].

This paper reports in particular an analysis conducted in the biomedical laboratories at the Sant'Andrea Hospital in Rome (one of the Italian node of the AOINM) aiming at investigating the integration of biomedical tools in telemedicine applications over the hospital LAN and WAN and the laboratory information system (LIS).

The study has two specific aims:
1. to design and construct a methodology useful to investigate:
- a specific biomedical tool, considering it as a complex, heterogeneous and distributed system (embedding parts of informatics, optics, complex elaborators etc.);
- the status of integration of a biomedical tool with the hospital LAN and WAN and the LIS;
- the available tools useful to improve the integration of the biomedical device with the hospital

N	Software/Toll	Documentation attached	Other information useful
1	Dasilab	☐	▬
2	Word	☐	▬
3	Adobe PDF writer	☐	▬
4		☐	▬
5		☐	▬
6		☐	▬
7		☐	▬
8		☐	▬
9		☐	▬
10		☐	▬
11		☐	▬
12		☐	▬
13		☐	▬
14		☐	▬
16		☐	▬

Fig. 1A | *A first example of the electronic module designed to gather information about the biomedical tool.*

LAN and WAN and the LIS (in order to obtain a partial or total integration);
2. to test the methodology on a representative bio-medical tool in a biomedical laboratory.

MATERIALS AND METHODS

The analysis in the laboratories was conducted by using an electronic module (EM) properly designed for the data collection and interviews to the personnel involved in the processes. Within this analysis, the technologies potentially available for the integration of the tools with the LAN/WAN have been considered:
- scanners (not only for glasses);
- electronic pens, capable to import in the PC the writing and thus capable to ameliorate the integration with the LAN, such as the anoto pen;
- speech to text converters, capable to convert the speech into electronic files ready for the integration with the hospital LAN, such as the Dragon Naturally Speaking 9.0 of the Nuance, or Loquendo ASR by Telecom Italia and IBM Via Voice 10.0;
- software-packages allowing an easy exchange of report with images, with a high level of security and privacy, such as Acrobat Pdf writer.

Figure 1A shows a sub-part of the section of the EM designed to get, in a structured manner, the list of equipments and/or software involved in a bio-medical tool.

Figure 1B shows a sub-part of a section of the EM designed to get, in a structured manner, the information about the status of integration with the LAN/WAN.

In the EM, the following tests were introduced as mandatory:
a) a test on the tele-service performance especially if implemented on a heterogeneous WAN architecture;
b) an acceptance test for operators in a context such as the daily or routine applications.

During the set-up of the study of digital cytology the authors found that the image played a core role. In particular the authors detected the following two areas of interest relevant to images:
A) images from equipments
- hystology (glasses- tissue);
- urines (glasses-sediments);
- hematology (glasses-strips).
B) image diagrams.

Also images from diagrams could be useful in digital cytology for the remote exchange in the activity of intranet and extranet for cooperative diagnosis, second opinion, e-learning and other applications. The most used diagrams are the cytometry and electrophoresis.

Figure 2 shows the area of interests of the digital cytology in terms of images from glasses and images from diagrams.

RESULTS AND DISCUSSION

Among the possible tools for telemedicine applications in the LAN/WAN the cytometry equipment [5] available in the technical unit of cytometry coordinated by one of the Authors (RA) has been considered useful for the integration. Cytometry is a technique that allows the measurement and characterization of cells in a fluid suspension. It is im-

Status of integration of the process with LAN/WAN

Is the toll integrated with the LAN/WAN?

Yes ☐   No ☐

Yes (it is integrated)

Describe in brief the modality of integration
▬

What kind of report does it furnish?
▬

Is it possible to obtain an electronic format of the report

Yes ☐ | No ☐

PDF ☐   Word ☐ | Possible actions?

Other ☐ ▬ | ▬

Fig. 1B | *Second example of the electronic module designed to gather information about the biomedical tool.*
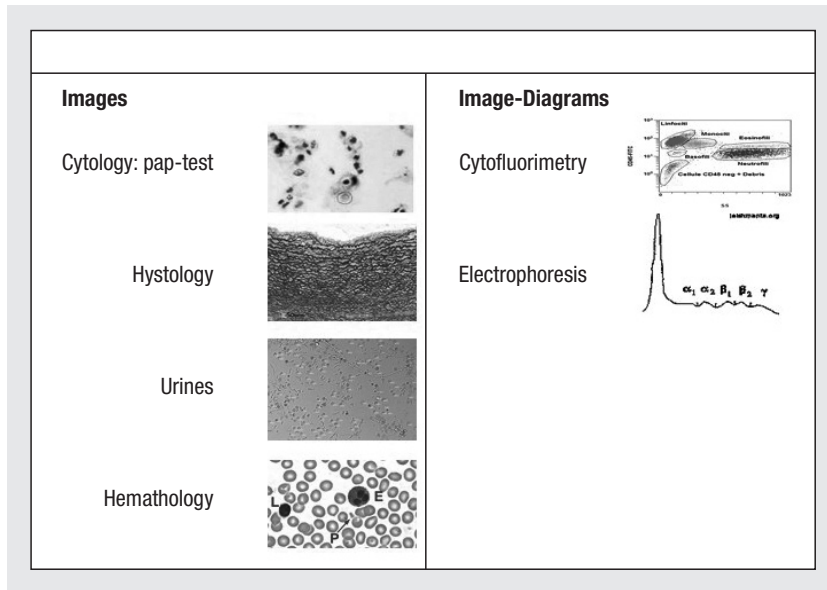
Fig. 2 | *Images useful to process in digital cytology.*

portant to point out that the analytical cytometry suffers from a lack of standardization for the integration into the hospital routine due to the unavailability of standard rules to convert files into digital imaging and communications and medicine (DICOM). In fact, though some attempts by researchers have been performed [6], the Working Group 26 of the NEMA (http://medical.nema.org/DICOM/minutes/WG-26/2009/2009-09-05/WG-26_2009-09-05_Min.doc) has only, as final aim, to face the integration of this discipline and is currently concentrated on the digital-pathology (see also the presentation by Bruce Beckwith in the within of the activity of the Working group 26 of the NEMA http://www.telepatologia.es/9ECT/presentations/Bruce_Beckwith.pdf).

The methodology allows the measurement of multiple properties of single cells at a high speed [7], and a detailed quantitative and qualitative analysis. *Figure 3* shows an example of diagrams from a cytometer. One of the field of application of cytometry is in the early detection of leukemia.

The analysis/diagnosis of a diagram (for example for the early detection of leukemia), is based on the experience of the biologist; several years of direct experience in the specific field are required. For this reason the methodology could benefit from the telemedicine support for the cooperative diagnosis or second opinion in tele-consulting. R. Amodeo has designed, prior to this study, a word-document useful to arrange meta-data comprehending word textual considerations and diagrams obtained after the data-mining conducted by the expert [9] *(Figure 4)*.

The study has investigated different software tools useful for the integration of the cytometry reports in a telemedicine application and chose Adobe Acrobat Writer for the requirements of security and privacy as the software for the integration.

This software has a high level of security which is concentrated on the file and not on the connection.

We should in fact consider that, because of remote exchange in telemedicine, the electronic report should be as secure as possible since the connection can be heterogeneous, starting from the hospital (Firewall,
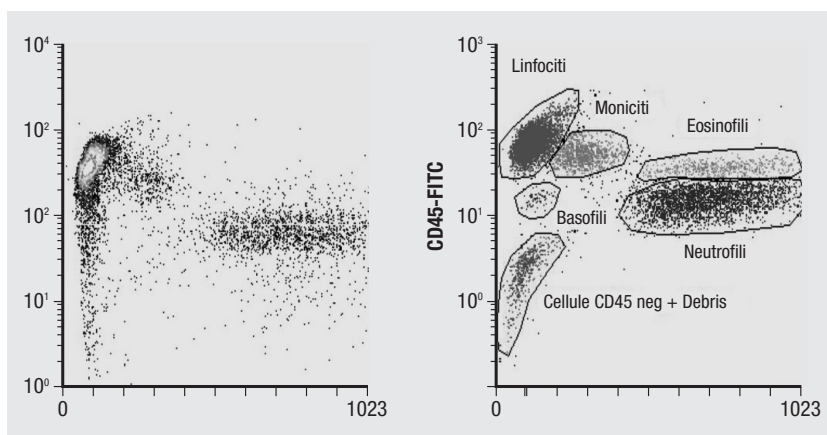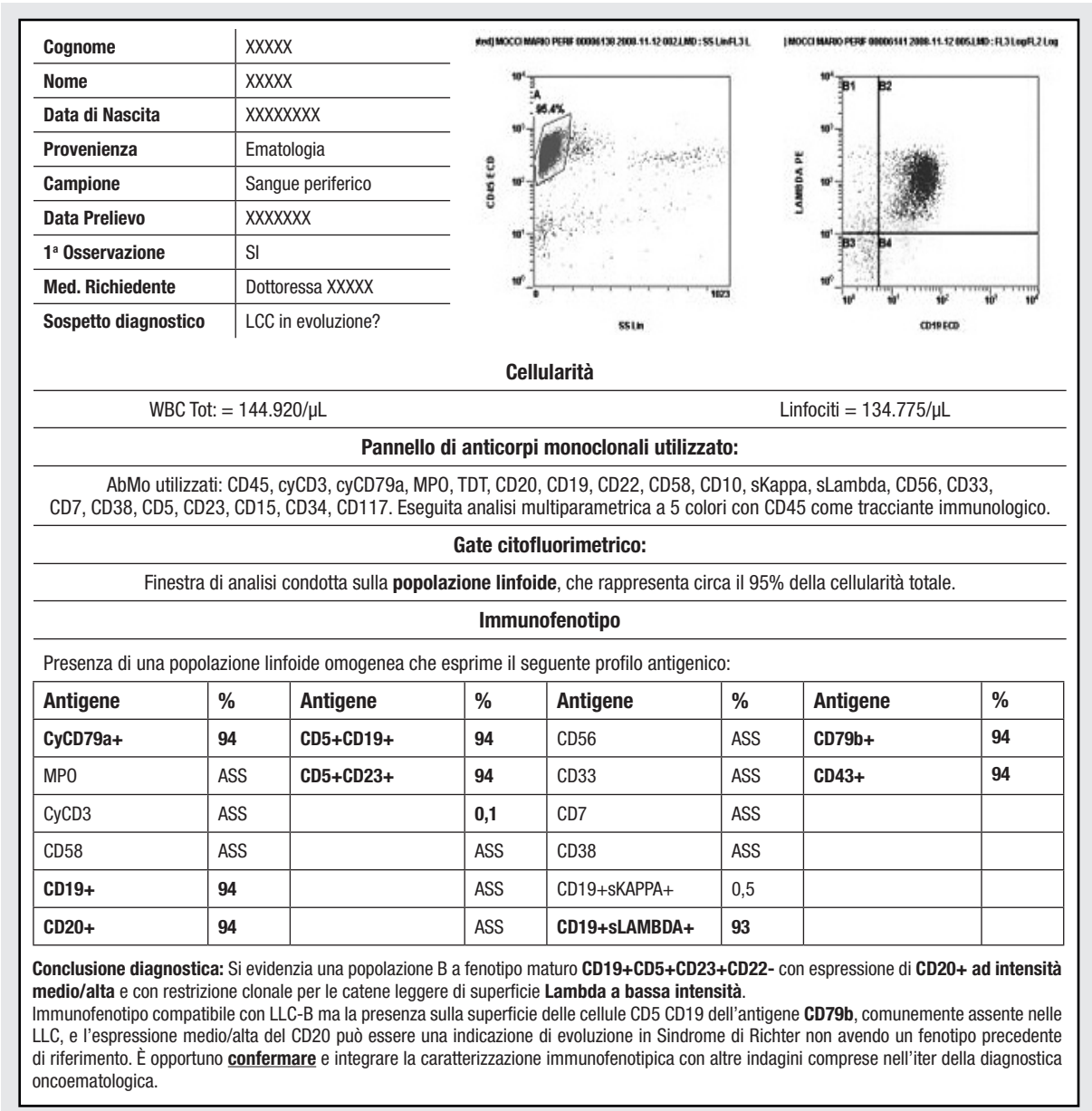

Fig. 3 | *Example of diagrams from a cytometer.*

Cognome	XXXXX
Nome	XXXXX
Data di Nascita	XXXXXXXX
Provenienza	Ematologia
Campione	Sangue periferico
Data Prelievo	XXXXXXX
1ª Osservazione	SI
Med. Richiedente	Dottoressa XXXXX
Sospetto diagnostico	LCC in evoluzione?

Cellularità

WBC Tot. = 144.920/μL   Linfociti = 134.775/μL

Pannello di anticorpi monoclonali utilizzato:

AbMo utilizzati: CD45, cyCD3, cyCD79a, MPO, TDT, CD20, CD19, CD22, CD58, CD10, sKappa, sLambda, CD56, CD33, CD7, CD38, CD5, CD23, CD15, CD34, CD117. Eseguita analisi multiparametrica a 5 colori con CD45 come tracciante immunologico.

Gate citofluorimetrico:

Finestra di analisi condotta sulla **popolazione linfoide**, che rappresenta circa il 95% della cellularità totale.

Immunofenotipo

Presenza di una popolazione linfoide omogenea che esprime il seguente profilo antigenico:

Antigene	%	Antigene	%	Antigene	%	Antigene	%
CyCD79a+	**94**	**CD5+CD19+**	**94**	CD56	ASS	**CD79b+**	**94**
MPO	ASS	**CD5+CD23+**	**94**	CD33	ASS	**CD43+**	**94**
CyCD3	ASS		**0,1**	CD7	ASS		
CD58	ASS		ASS	CD38	ASS		
CD19+	**94**		ASS	CD19+sKAPPA+	0,5		
CD20+	**94**		ASS	**CD19+sLAMBDA+**	**93**		

Conclusione diagnostica: Si evidenzia una popolazione B a fenotipo maturo **CD19+CD5+CD23+CD22-** con espressione di **CD20+ ad intensità medio/alta** e con restrizione clonale per le catene leggere di superficie **Lambda a bassa intensità**.
Immunofenotipo compatibile con LLC-B ma la presenza sulla superficie delle cellule CD5 CD19 dell'antigene **CD79b**, comunemente assente nelle LLC, e l'espressione medio/alta del CD20 può essere una indicazione di evoluzione in Sindrome di Richter non avendo un fenotipo precedente di riferimento. È opportuno **confermare** e integrare la caratterizzazione immunofenotipica con altre indagini comprese nell'iter della diagnostica oncoematologica.

Fig. 4 | *An example of cytometric report designed by the co-author R. Amodeo for the stand-alone recording.*

100 Mb/s of connection) it could reach also remote areas (no Firewalls, 56 Kb/s). Acrobat has proper functions of security and privacy and allows a lot of functions useful both to discipline the annotation of the pdf document (back-annotation) and to track the actions (and the responsible of) in a possible telemedicine application. It has been considered with particular interest the function which allows the automatic auto-deactivation of a document after a date; function that can strongly improve the security. Furthermore as well known, the pdf file reaches a good compression.

A number of delivering (N > 300) of the pdf documents obtained from the word document (with a memory occupancy lower than 500 Kb/s) have been performed in the WAN starting from the ISS LAN (100 Mb/s) up to ADSL-2 wireless connections. *Table 1* shows the outcome of an acceptance

Table 1 | *Acceptance test of the technology (max 3; min 0)*

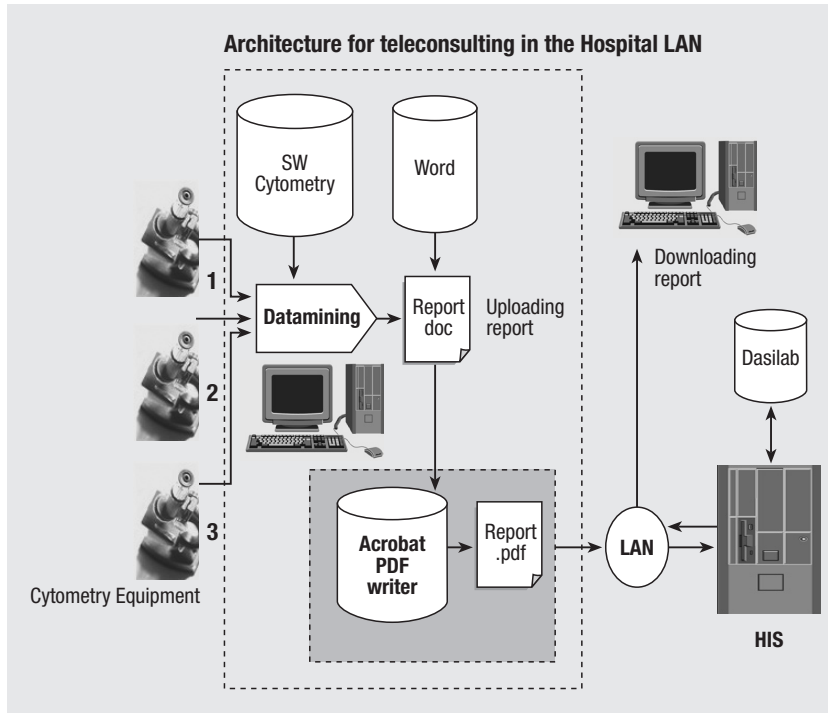| Item	Aspect	Score
1	User friendly	2.5
3	Speed of operations	1.9
5	Failure rate of operations	2.7

Fig. 5 | *Possible scenario of the tele-consulting in the hospital.*

test (performed by three experts in the field) of the solution as investigated on a link involving the ISS LAN (100 Mb/s, Firewall) and an ADSL-2 connection (10 Mb/s, no Firewalls) in the case of 30 randomized trials between the 8:00 a.m. and 6:00 p.m. The Hutten method [9] in the acceptance test has been used.

CONCLUSIONS

A study in the biomedical laboratory of the Sant'Andrea Hospital on the integration of bio-medical tools in telemedicine has been conducted. The study had in details two main specific aims:

a) to design and construct a methodology useful to investigate the biomedical tool considering it as a complex and heterogeneous system (embedding parts of informatics, optics, complex elaborators etc.);

b) to test the methodology on a representative biomedical tool in a biomedical laboratory.

From a global point of view the study detected as the image played always a basic role in the bio-
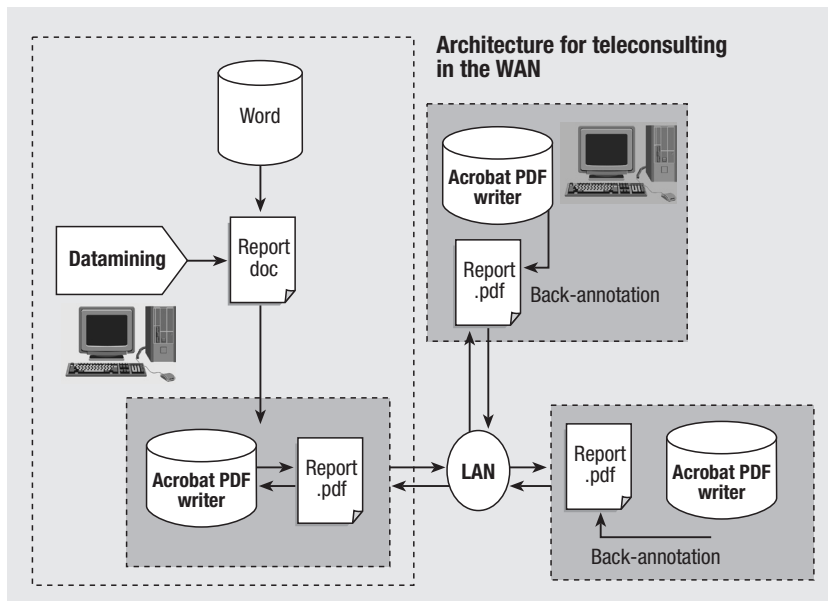

Fig. 6 | *Possible scenario of the tele-consulting in the WAN.*

medical laboratory both in the case of images from equipments (histology, urines and hematology) and in terms of images from diagrams (cytometer and electrophoresis).

The cytometry equipment (among the investigated biomedical tools) available in the technical unit of cytometry in the Sant'Andrea Hospital has been considered useful to be integrated for telemedicine applications. In fact the analytical cytometry suffers with a lack of standardization for the integration into the hospital routine due to the unavailability of standard rules to convert into DICOM (the Working Group 26 of the NEMA has only as final aim to face the integration of this discipline and is currently concentrated on the digital pathology).

The cytometry furnished thus a good chance to investigate the proposed methodology. The study ends with a technical solution based on the Adobe PDF writer package for the integration of cytometry reports both in the hospital LAN and the WAN in telemedicine. *Figure 5* shows a possible scenario in the LAN of the Sant'Andrea Hospital for internal tele-consulting; based on the LIS Dasilab (Dasit spa, Cardareto Milano, Italy, http://www.interconsultmd.com/soluzioni_software.html).

Figure 6 shows a possible scenario in the WAN for second opinion and tele-diagnosis applications.

The technical solution was successfully tested both in performance and acceptance on a link involving the ISS LAN (100 Mb/s, Firewall) and an ADSL - 2 connection (10 Mb/s, no Firewall) in the case of 30 randomized trials between the 8:00 a.m. and 6:00 p.m. The study considerations highlight the possibility and relevance of the integration of a biomedical tool for digital cytometry in telemedicine.

Conflict of interest statement

This paper is based on the work of a thesis at the Università Sapienza, Rome, Italy, by Marco Filoni, 2009.

There are no potential conflict of interest of any financial or personal relationship with other people or organizations that could inappropriately bias conduct and findings of this study.

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