




# Time-lapse imaging systems in IVF laboratories: a French national survey

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## Abstract

**Purpose** Although the clinical value of time-lapse imaging (TLI) systems in in vitro fertilization (IVF) cycles is still debated, its prevalence worldwide seems to be expanding. The situation of TLI in the USA has been recently surveyed, but these results might not be transposable to other countries with different IVF regulation and funding such as France. This study evaluated the TLI situation in French IVF laboratories.

**Methods** An anonymous online cross-sectional survey was sent by email to 210 embryologists in September and October 2017. Laboratories, demographics, TLI clinical use, purchasing plan, and embryologists' opinions were analyzed using logistic regression to calculate odds ratio.

**Results** Of the 210 lab directors surveyed, 78 responded (37.1%), 43 (55%) working in private IVF laboratories and 35 (45%) in public hospitals. Thirty (38.5%) were TLI users. The odds of TLI possession were not statistically different according to laboratory sector or size. Most embryologists ( $n = 21$ , 70%) used TLI for unselected patients. Cost was the main reason given by non-users for not implementing TLI ( $n = 24$ , 50%). Most respondents were convinced that TLI is superior to standard morphology ( $n = 52$ , 73.2%) and that TLI improves culture conditions ( $n = 62$ , 84.9%). However, half ( $n = 39$ , 54.9%) indicated that evidence was still lacking to assert TLI clinical usefulness.

**Conclusion** The prevalence of TLI systems and embryologists' opinion in France was slightly different from the American situation. The different regulation and funding policy might account for some differences in terms of TLI use and perception.

**Keywords** Assisted reproductive technology · Time-lapse imaging · Morphokinetic · Cross-sectional survey · Embryo selection · In vitro fertilization

## Introduction

In a context of growing in vitro fertilization (IVF) activity worldwide, major challenges face infertility specialists. Selecting the best embryo with the highest implantation potential for transfer in order to shorten time to pregnancy, while

reducing the risk of multiple gestations and their associated medical, economical and psychological consequences, is one of them. Static morphological evaluation of embryos has some limitations, such as embryo exposure to suboptimal culture conditions, limited predictive value for ploidy status and implantation and perfectible inter- or intra-observer agreement. However, it still remains the method of choice for embryo quality assessment in the majority of IVF laboratories and the primarily validated method in ESHRE consortium guidelines [1].

Time lapse imaging (TLI) of embryos has been developed in humans and animal models more than 2 decades ago [2–4], but commercial devices specifically designed for human IVF were first launched in the early 2010s. TLI systems offer the advantages of optimized embryo culture conditions, continuous monitoring of embryo development and lower inter-observer variability [5–11]. Although TLI market appeared to be fast-growing over the last 5 years, with some promising research papers and positive feedback by several embryologists and patients, the additional clinical value and cost-

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effectiveness of using morphokinetics to improve embryo selection still remains a matter of debate in the international literature [8, 12–19]. Indeed, its predictive ability of embryo ploidy status or implantation has been questioned [17, 18]. However, some recent studies and meta-analysis seem to raise the possible association between morphokinetic and clinical outcome [11, 16].

In this respect, it is interesting to note that very little data are available on the current prevalence and clinical use of TLI in IVF laboratories worldwide. Furthermore, the embryologists' opinion regarding the clinical value of TLI and its place in modern IVF daily practice has hardly ever been reported. Interestingly, Dolinko et al. (2017) [20] very recently reported that TLI systems' possession in IVF laboratories in the USA was low, with only one out of five laboratory directors reporting a positive opinion on TLI technology. However, these results might not be transposable to other nations, as ART regulation and funding hugely differ among countries, potentially deeply influencing IVF specialists' and patients' opinions and willing to pay for innovations. France is the largest IVF market in Europe, with 105 IVF centers (approximately half public and half private) performing > 61,000 cycles every year [21]. French funding system of ART is very specific, as all expenses related to ART, including infertility workup, medications, ovum pickup, and embryology procedures are fully covered by the national social security system, both in public and private settings. The list and price of the procedures that are reimbursed is fixed by the government, and laboratories do not receive additional income when extra procedures such as TLI are used, unless they charge patients, which is very unusual. Previous study reported that TLI implementation, as well as embryologists' opinions, was different depending on laboratories' demographic and TLI possession. It is therefore interesting to investigate these factors in the French specific IVF legal and financial context.

The purpose of our study was to survey the prevalence of TLI possession in France and French embryologists' opinions and their motivation or reluctance to invest in this technology.

## Methods

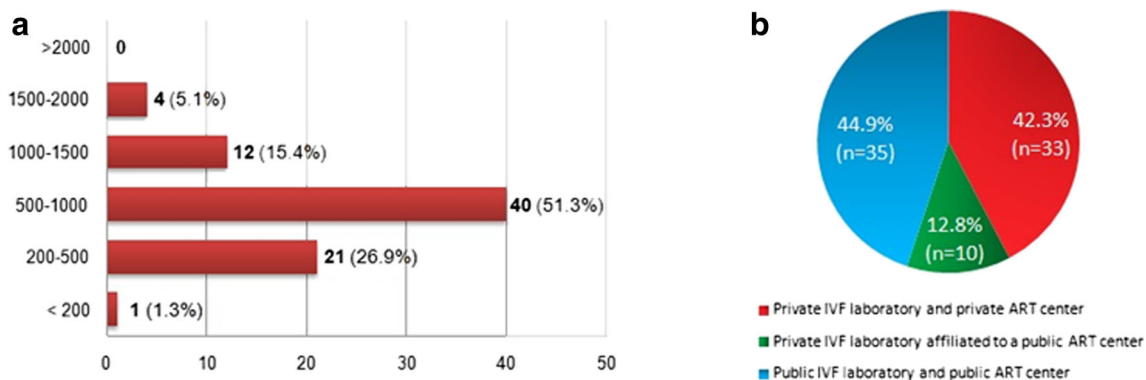
An anonymous online survey freely inspired from the study by Dolinko et al. (2017) [20] was designed and sent by email to the 210 French IVF laboratories directors and senior embryologists members of the national BLEFCO network (main French clinical embryology organization grouping private and public sectors, 105 laboratories in France) and included in BLEFCO mailing list (survey available as [supplementary material](#)). This online survey consisted in 28 items including categorical, yes/no, multiple choice, and open questions. Moreover, respondents had the opportunity to add free comments after yes/no and multiple choices questions. The survey was structured in four main topics: (1) demographics of the IVF laboratories, (2) TLI system(s) possession in the IVF laboratories, (3) TLI system(s) use, and (4) opinion on the TLI technology. This online survey was sent by email in September and October 2017. The online survey was kept opened for 6 weeks, with one reminder email sent in October 2 weeks before closing. All data were acquired and automatically exported in Excel spreadsheet for analysis.

Statistical analysis consisted in logistic regression to calculate odds ratio (OR) and 95% confidence intervals (CI). All the calculations were done with R software, version 3.4.2. (<http://www.Rproject.org>). Odds were considered significant at  $p < 0.05$ . All the data including open responses data were compiled and unified by a single author (TB).

## Results

### Demographics of TLI use

The overall response rate of the survey was 37.1% ( $n = 78$  respondents/210). The professional characteristics of the survey respondents are presented in Fig. 1. The majority of them practiced in IVF laboratories performing 500 to 1000 oocytes retrievals a year (Fig. 1a). A total of 58% of the respondents worked in a private setting, while 42% worked in a public



**Fig. 1** Professional characteristics of the respondents, with the annual number of oocyte retrievals in their laboratory (a) and their practice setting (b)

setting (Fig. 1b). This is relatively a representative of the overall repartition of IVF units in France. A total of 30 embryologists (38.5%) reported using at least one TLI system in their laboratory, with 4 of them (5%) using several systems. The median number of TLI systems used by the respondents was 1 (total range 1–4). EmbryoScope© was the most implemented TLI system ( $n = 14$ , 46.7% of TLI users), regardless of the number of TLI systems in the laboratory. Geri©, Primo Vision©, and Miri© systems were used by seven (23.3%), six (20%), and three (10%) of the TLI users respectively. No respondent reported using two different TLI systems. The odds of TLI use were not statistically different according to IVF center size or sector (private or public) (Table 1). Among the 30 TLI users, 4 (13.3%) planned to invest in additional devices. The remaining 48 respondents (61.5%) reported that they were not currently using any TLI system. Among them, about half had no intention to invest in this technology ( $n = 25$ , 52%), while 23 (48%) had plans to buy at least one TLI system in the near future. Concerning financial aspects, the majority of the TLI systems ( $n = 16$ , 53.3%) were exclusively purchased from laboratory own funds, while nine (30%) were purchased from clinic or hospital research or equipment budget, and five were either loaned ( $n = 1$ , 3.33%) or partially funded by the manufacturer ( $n = 4$ , 13.3%). Among non-users, half ( $n = 24/48$ , 50%) reported that the main reasons for not investing in TLI technology was its cost. The other main reason given by non-users was the lack of published data supporting the clinical value of TLI ( $n = 18$ , 37.5%).

### Conditions and indications of TLI system use

Among TLI users, the majority of them ( $n = 21/30$ , 70%) reported using TLI for both positive embryo selection for transfer and exclusion of poor prognosis embryos. Among others, seven (23.3%) and two (6.7%) embryologists reported using

TLI for embryo selection or exclusion respectively, and three (10%) reported using TLI mainly for research. The majority of TLI users ( $n = 20$ , 66.7%) reported using TLI for evaluation of embryos at both cleavage and blastocyst stages, while three (10%) used TLI exclusively for embryo selection at the cleavage stage, and eight (26.7%) for embryo selection at the blastocyst stage. Among TLI users, most embryologists ( $n = 21$ , 70%) use TLI for unselected patients, whatever their prognosis in ART or history. Conversely, seven (23.3%) give preference to poor prognosis patients and two (6.7%) to good prognosis patients. Among the 30 TLI users, only 4 (13.3%) reported charging extra fees to patients for TLI use, with charges ranging from 85€ to 250€ per cycle (approx. \$100 to \$300). All of them worked in a private IVF laboratory, part of a private ART center.

### French embryologists' opinions on TLI

The majority of respondents were convinced that morphokinetic is a better embryo quality assessment method than conventional morphology ( $n = 52$ , 73.2%) and that it improves embryo culture conditions ( $n = 62$ , 84.9%). Moreover, most respondents believe that TLI systems provide better information not only for embryologists, but also for patients and/or clinicians ( $n = 48$ , 66.7%), and that TLI technology represents a potentially useful tool for the management of patients undergoing IVF cycles rather than a communication and advertisement support ( $n = 44$ , 61.1%). However, half respondents ( $n = 39$ , 54.9%) reported that strong evidence is still lacking on the clinical usefulness of TLI systems in IVF, and 44 (62%) doubted that TLI will soon become the gold standard for embryo selection in IVF laboratories.

TLI users had significantly greater odds to consider TLI as a better embryo selection tool, providing better embryo culture conditions and being potentially clinically useful than

**Table 1** Odds of TLI system use by respondents based on clinic volume by annual number of oocyte retrievals and sector of practice

Biologists demographics	Biologists using TLI system(s) ( $n = 30$ )	Odds ratio of TLI possession (95% CI)
Number of oocyte retrievals/year		
• 200–500	9/22 (40.9%)	Referent
• 500–1000	13/40 (32.5%)	0.72 (0.24–2.15)
• 1000–1500	6/12 (50%)	1.44 (0.35–6.10)
• 1500–2000	2/4 (50%)	1.44 (0.15–13.96)
IVF laboratory sector		
• Public laboratory	16/35 (45.7%)	Referent
• Private laboratory	14/43 (32.6%)	0.54 (0.21–1.37)
Hospital and/or clinic sector		
• Public	18/45 (40%)	Referent
• Private	12/33 (36.4%)	0.83 (0.32–2.08)

non-users ( $p < 0.05$ ). However, odds to agree to the remaining statement opinions were not significantly different in term of TLI possession (Table 2).

Among the 52 respondents reported being convinced that morphokinetic was a better embryo quality assessment method than conventional morphology, 42 gave one or more specific reasons, with 29 (55.7%) citing the benefits of recording morphokinetic data, mentioning the interest of easily observing abnormal cleavages ( $n = 8$ , 15.4%) or abnormal fertilization ( $n = 3$ ), and 2 highlighting the possibility to retrospectively grade embryos at precise timings, especially when this should theoretically be performed very early in the morning.

## Discussion

The purpose of our study was to evaluate the implementation of TLI systems in French IVF laboratories and French embryologists' opinion regarding this technology. The French IVF market is peculiar, as all direct costs related to IVF (medication, laboratory procedures except innovations such as TLI) are fully covered by the government according to fixed prices, thus constituting an interesting environment to study embryologists' opinion and motivations to invest in innovative but expensive technologies such as TLI.

We found that the prevalence of TLI systems in France was significant among respondents (38.5%). Moreover, half of non-users were planning to invest in TLI in the near future, highlighting the interest of French embryologists for this technology. This is in slight contrast with the US situation where the proportion of potential future investors was lower, as recently reported by Dolinko et al. [20]. This could be considered quite surprising when the financial is taken into account. Indeed, US laboratories generally charge patients for all or part of the costs related to IVF (except in case of specific insurance coverage), as opposed to France where laboratories'

income is fixed by law and only depends on the amount of cycles performed. This could theoretically allow US laboratories to repay TLI investment and facilitate its amortization; therefore, lowering the financial risk and reluctance to invest in this expensive technology. However, Dolinko et al. [20] reported that only a minority of US laboratories were specifically charging patients for TLI (28%). Anyway, our results suggest that IVF funding policy does not seem to impact TLI implementation rate and embryologists' opinion on it.

As in US laboratories, half TLI systems in France were exclusively purchased on the laboratory's own funds and EmbryoScope© was the most frequently used TLI system. However, the odds of TLI system use in France were not significantly associated with the annual number of IVF cycles performed or with private sector, contrary to American results. It should be noted that the relatively limited number of respondents on our French survey might prevent from reaching statistical significance. The majority of French TLI users reported using this technology for the selection of embryo for transfer and for the exclusion of embryos with very poor prognosis, as reported in the Dolinko et al. study [20]. It should be noted that the survey's items did not specifically assess the criteria used by the embryologists to either select or discard embryos with abnormal morphokinetic patterns. Respondents also reported offering TLI to all of their patients, whatever the type of procedure (IVF with or without ICSI) or their prognosis, while few of them charged patients. This is quite similar to the American situation as well [20].

Despite these apparent similarities, some differences could be noted between French and American embryologists, especially in terms of opinion on the TLI technology and its clinical value. Indeed, most of French TLI users were convinced of its superiority over standard morphology in terms of embryo culture conditions, patients' and clinicians' information, and clinical outcome. The reasons underlying these differences are unclear and might be explored in more details in further studies in various countries.

**Table 2** Biologists' opinions on the TLI technology based on reported usage of a TLI system

Survey items	Non-users ( $n = 48$ )	TLI users ( $n = 30$ )	Odds ratio of agreement (95% CI)
TLI is superior to standard morphology	25/44 <sup>a</sup> (56.8%)	27/29 (93.1%)	10.26 (2.62–68.60)*
Available literature supports the clinical use of TLI	15/42 (35.7%)	17/29 (58.6%)	2.55 (0.98–6.89)
TLI will soon become the gold standard for embryo quality assessment	13/43 (30.2%)	15/29 (51.7%)	2.47 (0.94–6.70)
TLI provides better information not only to embryologists, but also to clinicians and/or patients	28/44 (63.6%)	21/29 (72.4%)	1.50 (0.55–4.31)
TLI improves embryo culture conditions	33/44 (75%)	29/30 (96.7%)	9.77 (1.72–182.08)*
TLI is a communication and advertisement tool rather than a clinically useful tool	24/43 (53.8%)	4/30 (13.3%)	0.12 (0.03–0.38)*

<sup>a</sup> Number in agreement/number of respondents. \*Significant odds ratio and confidence intervals ( $p < 0.05$ )



Whether IVF coverage influences IVF use rate, the number of IVF cycles performed and the techniques used has been questioned in some studies and is a matter of concern for stakeholders and decision-makers. The recent example of Quebec where full state funding for IVF implemented in 2010, with a significant increase in activity and modification in practice, before being stopped in 2015, leading to a significant decrease in IVF activity, is exemplary [22, 23]. Likewise, insurance coverage mandates have been shown in USA to influence ICSI use for non-male-factor infertility cycles [24]. International studies comparing ART use in various countries with different funding policies would help evaluating the association between the economic context and medical practice. Anyway, the most cost-effective funding policy still remains to be identified.

In this study, embryologists were asked about their opinion regarding the clinical value of TLI systems. The majority of them were convinced that TLI was a better embryo quality assessment method than conventional morphology and that it improved embryo culture conditions, making it a useful tool for embryologists, patients, and clinicians. In particular, TLI has been shown to provide a high agreement between and within observers, regardless of the TLI system, where static morphological embryo assessment is not optimal [9, 10, 25]. Combined with the advantage of continuous monitoring in stable conditions, TLI may improve daily practice, help reducing risks of non-correct assessments regardless of embryologist's experience, training junior embryologists, and ultimately homogenizing decision-making process [26]. TLI also allows improving the assessment of abnormal fertilization. However, many respondents also reported that strong evidence was still lacking on the effective clinical value of TLI, and doubted that TLI would soon become the gold standard for embryo selection in IVF. This apparent gap between opinions and scientific evidence is not surprising and reflects the ongoing debate in the literature on the clinical value of TLI. In daily IVF routine, embryologists have the responsibility to choose which embryo(s) within a cohort should be used for transfer (and freezing) in order to reach the highest success rate for patients. They also have to decide which embryo(s) should be rejected because of their poor implantation potential. In this respect, the gold standard method for embryo quality assessment is based on daily observations of embryo morphology, whose limitations have been largely described, including subjectivity and relatively poor association with embryo implantation potential. As preimplantation genetic testing for embryo aneuploidy screening (PGT-A) has been also promoted, but its real clinical efficacy is still questioned. Moreover, this technology is expensive and suffers from regulatory issues in some countries (including France). In this context, TLI has raised hope for several groups as a non-invasive embryo quality assessment method allowing

improving embryo selection or deselection for transfer. TLI does not provide a binary response concerning embryo ploidy status, but morphokinetic parameters, alone or in combination, may be associated with embryo implantation potential. However, the search for highly predictive morphokinetic parameters and their clinical validation in prospective randomized controlled trials (RCTs) is still ongoing [11]. Early promising studies [27] were rapidly criticized, and even further RCTs [28] were questioned [29, 30]. It is indeed intriguing that despite all these comments on the studies' limitations, the "ideal" RCT answering the pending questions on TLI clinical value still remains to be reported. Although meta-analysis could be expected to provide a relevant conclusion, the heterogeneity of their methodology and of the studies included lead to discordant conclusions [16]. In this context, many embryologists might prefer waiting for more evidence-based studies before investing in this technology. It would thus be interesting to repeat this survey in a few years, as more robust evidence on TLI clinical value will undoubtedly soon become available.

We acknowledge that this study has some limitations. First, the use of voluntary surveys exposes to the risk of over representation of pros, i.e., TLI users, among respondents. However, the average response rate observed here might limit the impact of this bias on our analysis, even though the absolute number of respondents was quite limited. We acknowledge that such a response rate exposes to a theoretical risk of bias, but this is inherent to this kind of study. Second, it is difficult to speculate why some people did not respond despite receiving a reminder by email. We cannot exclude that some email distribution problems occurred, although the mailing list is routinely used and updated by the Blefco national embryology network. Third, this anonymous survey was sent to at least one embryologist per IVF center, regardless of the affiliation. Therefore, it could have been filled out by several embryologists working in the same ART center, although this was discouraged in the recommendations. However, the population of respondents is representative of French IVF laboratories in terms of setting and number of oocyte retrievals [21]. Lastly, the survey we used was inspired from the one published by Dolinko et al. [20], but it was not strictly comparable. In this respect, the comparison between the French and the American situation should be interpreted with care.

In conclusion, this study described the current use of TLI in France, as well as embryologists' opinions, on this technology. We found that TLI use in France was quite similar to its use in USA, despite of very different funding policies. Comparing embryologists' opinion and the implementation of innovative and expensive technologies such as TLI systems in various countries with different regulations and funding sources might be of interest and provide relevant elements for embryologists and decision-makers when considering an investment in such innovations.

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